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CHOLECYSTITIS: A BACTERIOLOGIC AND EXPERIMENTAL STUDY OF THREE HUNDRED SURGICALLY RESECTED GALL BLADDERS[1]

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VIABLE bacteria have been isolated by different investigators, from surgically resected gall bladders that have been the site of cholecystitis. That some of these bacteria are causative is shown by the fact that they produce lesions of the gall bladder when injected into experimental animals. This has been shown by various investigators (2, 4, 6, 7, 10, 11, 12). Some have been unable to duplicate Rosenow's results whereas others, such as Wilkie, have reproduced his results, culturally as well as experimentally. Wilkie has isolated, as has Rosenow, the causative streptococcus in the biliary lymph node as well as in the wall of the gall bladder in a very high percentage of cases. He also has reproduced the lesions in rabbits in a striking manner, by injecting the streptococcus in different ways.

Recently at The Mayo Clinic we have made cultures from 300 consecutive gall bladders, using Rosenow's technique, and in some instances Wilkie's modification. The cultures were made irrespective of the reasons for removal of the gall bladders and irrespective of the amount of pathological change visible. Twenty-three per cent of the patients were men; 77 per cent were women of whom 89 per cent were married. Many of the women gave a history of cholecystitis starting or recurring shortly after childbirth. Most of the patients were more than 40 years of age; the youngest was 19 years of age, and the oldest 77 years. The majority (85 per cent) of all of these patients had potential foci of infection, such as pulpless teeth, chronic lacunar or follicular tonsillitis, prostatitis, endocervicitis, and sinusitis. The majority of those who returned to The Mayo Clinic later for re-examination still retained such foci even though there were consultant's notes on the charts advising their removal.

The cases were divided into four groups according to the symptoms (tabulation). Any patient who had a typical history of disease of the gall bladder was placed in group 1 or 2. If the condition was of 4 months' duration or less, the patient was placed in group 1; if of more than 4 months' duration, in group 2. Group 3 included those patients who had indistinct or vague symptoms not exactly typical of disease of the gall bladder. Group 4 included those patients in whom a stone in the cystic or common bile duct was the essential finding. According to this classification, there were 6 cases in group 4, in 3 of which cultures made from the gall bladder were sterile and in the other 3 of which the predominating organism was a gram-negative bacillus; in none was a streptococcus found. There were 116 patients in group 3, and cultures made from 75

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of the gall bladders (65 per cent) were sterile; of the remaining 41 cultures, the predominating organisms were staphylococci and various bacilli. In only 8 of the 41 was there a green-producing or indifferent streptococcus. There were 82 cultures of gall bladders of patients from group 2, 40 of which were sterile and 42 of which contained streptococci, staphylococci, or bacilli. Group 1 consisted of 96 cultures and only 32 per cent were sterile. Of the 64 positive cultures in group 1, 45 (70 per cent) contained streptococci; 35 of the 45 were pure cultures of streptococci. Thus, in group 1, in which one would expect good cultural results if the bacteria are of etiological significance, 68 per cent of the cultures were positive, with streptococci predominating. In group 2, in which the condition had become chronic, 51 per cent of the cultures were positive. In group 3, in which most of the symptoms were vague and indistinct, only 35 per cent of the cultures were positive. In group 4, in which obstruction to the ducts was the main finding, 50 per cent of the cultures contained a bacillus, but in no instance was a streptococcus isolated.

Altogether cultures were made from 300 gall bladders of which 150 (50 per cent) were sterile. Of the 150 cases in which the cultures were positive, in 66 (44 per cent), the predominating organism was a streptococcus; in 45 (30 per cent), a bacillus; and in 39 (26 per cent), a staphylococcus or other related cocci.

In this series of 300 gall bladders there were 65 "strawberry" gall bladders of which 46 (71 per cent) were sterile. From 9 gall bladders a streptococcus was isolated; from 7, a bacillus; and from 3, staphylococcus albus. In most of the cases in which a positive culture was obtained from "strawberry" gall bladders, there also was a complicating factor such as a stone in the cystic or common bile duct, or there was perihepatitis definite enough to be mentioned in the surgeon's report.

We also made cultures from numerous cystic lymph nodes. Cultures therefrom approximately paralleled those obtained from the walls of the gall bladders.

The streptococci usually produced distinct, green colonies on blood agar, often requiring a gradient of oxygen tension for growth. The majority did not grow on a streaked blood-agar plate until after at least one culture had been made in glucose-brain broth. The bacilli were mainly gram-negative bacilli; usually, they fermented dextrose, but the reactions of fermentation were variable in the other sugars. In three instances the reactions in sugars were those of typhoid bacilli. In a few instances, a gram-positive, spore-bearing bacillus was isolated. This was considered either a contaminant or a secondary invader, since it never produced any gross lesions in rabbits. According to the reactions in sugars, the streptococci most frequently isolated were streptococcus fæcalis and streptococcus mitior. The other two types encountered to a lesser extent were streptococcus non-hæmolyticus 1 and 3. Neither the streptococci isolated from the bile or from the wall could be placed in any particular group, since all the strains were isolated at times only from the wall, at other times only from the bile, and at times from both the wall and the bile. Much stress has been placed recently on the relationship between streptococci and enterococci. As yet there is no definite agreement as to what constitutes an enterococcus. Some German authors (5) believe the enterococcus to be a variant of streptococcus viridans. Practically all of the strains that we have isolated are not enterococci according to the standards as summarized by Dible. They belong rather to the streptococcus viridans group, called green-producing streptococci by Rosenow to distinguish them from the streptococcus viridans lenta described first by Schottmueller.

Whenever extensive hæmorrhagic cholecystitis or marked empyema of the gall bladder was encountered, cultures therefrom almost invariably contained a gram-negative bacillus, alone or in mixture with the streptococcus, and the gram-negative bacillus usually fermented dextrose. According to cultural and experimental results, staphylococcus albus was considered more often a coincidental than a causal factor, although in some instances the staphylococcus could not be considered a contaminant. Frequently, in making cultures from the wall of the gall bladder, we dissected off a piece of serosa and muscle and made a culture from it separately. We then, also,

made a culture from the remaining portion of the wall, consisting largely of the mucosa, after it had been washed in sterile solution of sodium chloride. It sometimes happened that cultures of the outer portion of the wall contained staphylococci alone or staphylococci mixed with streptococci, or bacilli, whereas the mucosal portion of the wall was sterile or contained the streptococci or bacilli without the staphylococci. This also was true of bacillus subtilis in a few instances. Consequently, we feel that sometimes at least, bacillus subtilis and staphylococcus albus were contaminants. In this respect our results correspond with those of Mestitz and Rittner, who examined smears and sections of the gall bladder immediately after surgical removal of the gall bladder and again after culturing the tissue. They found that in some cases in which the direct examination was negative, cultures showed staphylococci, or in cases in which the direct examination showed other organisms, after incubation the tissues showed the other organisms and staphylococci.

It is known that bile inhibits the growth of organisms, especially streptococci. In our experience it did not do so unless present in rather large amounts. This seems to be contrary to the experience of Wilkie. In only one instance did the outer portion of the wall yield a streptococcus when the inner portion remained sterile, and the growth of this streptococcus was not inhibited when 5 drops of the bile were added to 15 cubic centimeters of the culture medium before it was inoculated with 2 drops of a culture of the streptococcus in question. In tubes containing the macerated tissue of the gall bladder we have often added, with a Pasteur pipet, up to 10 drops of bile (later proved sterile) from the same gall bladder and have found that in the tubes which contained the bile the streptococcus and other organisms grew as well as in those to which bile had not been added. This was true no matter if the sterile bile came from gall bladders the walls of which contained streptococci, or were sterile. After we had determined this fact often enough to convince ourselves, we discontinued culturing the wall piecemeal and simply washed the tissue in several changes of sterile solution of sodium chloride.

The number of our positive results in this series is not as high as that obtained several years previously with the same technique, nor as high as that obtained by Rosenow or by Wilkie. One of us (9) has reported previously that tetiothalein sodium-N.N.R. (iodeikon) has a marked bacteriostatic action for streptococci, and we thought that its extensive use for diagnostic purposes at The Mayo Clinic in the last 2 to 3 years might be responsible for the lowered incidence of positive cultures. Thus, we determined the time interval between the giving of the dye and the making of the cultures from the resected gall bladders in the cases with negative cultures on the one hand and in those with positive cultures on the other hand. Ninety-nine, or approximately a third of the patients, did not receive dye. Most of these 99 cases, in which bacteria, especially streptococci, were found, were classified in group 1; in these cases rather acute conditions prevailed and a dye test was not advisable or necessary. In contrast, the majority of negative cultures in the 99 cases were from group 3, in which the symptoms were not typical of cholecystitis.

Of the 201 remaining patients who received the dye, the time interval in days between the giving of the dye and the making of the culture from the gall bladder was determined. This time interval was least in the group in which cultures remained sterile, and was 8.2 days. In the group in which a bacillus was isolated, the time interval was 8.4 days. In the group in which various forms of staphylococci and diphtheroid organisms were isolated, the time interval was 10.4 days, and in the group in which a streptococcus was isolated, the average time interval was 11.2 days, whereas in the group in which the streptococci were isolated in pure culture the average time interval was 12.8 days.

Rabbits were given intravenous injections of freshly isolated cultures of the various organisms, both with pure cultures and with mixed cultures, according to the technique described in previous publications. The animals usually were given injections on three successive days and were allowed to live from 1 to 6 weeks. During the experiments we discovered, as Cecil had discovered in experi-

Fig. 1. Empyema of the gall bladder of a rabbit 7 days after two intravenous injections with 4 and 5 cubic centimeters, respectively, of a 24-hour glucose-brain-broth culture of streptococci obtained from a surgically resected gall bladder.

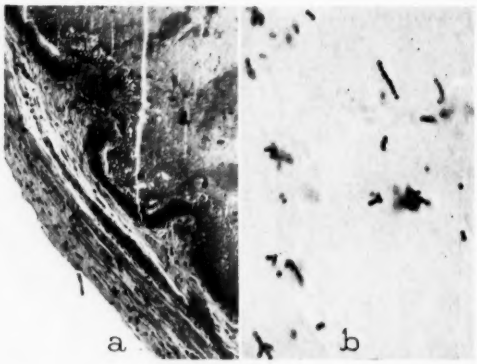

Fig. 2. *a*, Section of the wall of the gall bladder shown in Figure 1. There is swelling and necrosis of the cells of the tips of the villi (hæmatoxylin and eosin, ×150); *b*, streptococci in the necrotic tip of the villus (Gram-Weigert stain, ×1000).

ments on animals with arthritis, that repeated injections, even though small, over a longer period of time, produced better results in many instances. In our experience, pure cultures of staphylococci never produced cholecystitis; neither did cultures of so-called diphtheroid organisms unless the diphtheroid organisms were streptococcus variants as evidenced by subcultures. In practically every culture of a gall bladder that had been the site of empyema, and that had markedly thickened walls, and in cultures of hæmorrhagic, gangrenous gall bladders, a gram-negative bacillus was isolated, sometimes in pure culture and often mixed with a streptococcus. When such freshly isolated cultures were injected into rabbits in small doses (bacilli of the colon group are quickly fatal to rabbits) they sometimes also tended to produce hæmorrhagic gangrenous cholecystitis. In the rabbits that received injections of cultures of the streptococcus, focal lesions of the gall bladder often developed within 24 hours. However, in order to produce chronic indurated lesions, or cholelithiasis, 3 to 5 weeks were needed. In this respect, the colon bacillus differs from the streptococcus because the colon bacillus usually produced mucopurulent bile, with necrosis of the wall, in a shorter time.

Altogether 72 strains were injected into rabbits. Forty-one strains contained the streptococcus in large numbers and 28 (68 per cent) of these localized in the gall bladder of the rabbit. In contrast, none of the strains of staphylococcus albus, and only 5 of the 31 strains in which the streptococcus was absent, or present only in very small numbers, localized in the gall bladder of the rabbit. Seventy-eight rabbits were given injections of these 41 strains containing the streptococcus, and in 35 (45 per cent) lesions of the gall bladder developed. In contrast, 54 rabbits were given injections with the 31 other strains, and in only 5 (9 per cent) lesions of the gall bladder developed. Altogether, 132 rabbits were given injections of cultures obtained from the surgically resected gall bladders and in 40 (30 per cent) lesions of the gall bladder developed. The highest incidence of localization elsewhere in the body was in the joints (2 per cent). These percentages are comparatively low, but it must be remembered that the majority of such experimental lesions are self-healing. Consequently, in our endeavor to produce marked and more chronic evidence of cholecystitis as well as of cholelithiasis, the animals were allowed to live for a long time, and during this time the more

Fig. 3. Hæmorrhagic empyema of the gall bladder of a rabbit with adherent necrotic omentum, 28 days after two intravenous injections of 5 and 6 cubic centimeters of a 24-hour culture of a mixture of streptococci and colon bacilli isolated from a surgically resected gall bladder.

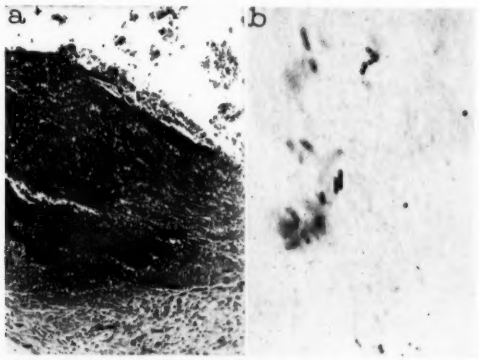

Fig. 4. *a*, Section of the wall of the gall bladder shown in Figure 3. The wall is thickened and there is marked cellulitis, with necrosis of the infiltrated tissue (hæmatoxylin and eosin, ×80); *b*, colon bacilli and streptococci found in the necrotic area shown in *a* (Gram-Weigert stain, ×1000).

superficial and acute lesions healed. Notwithstanding this, including all the strains injected, some of which undoubtedly were contaminants, the percentage of specific localization in the gall bladder was approximately ten times that obtained when specific strains isolated from patients with other diseases were employed.

The following results illustrate the various types of experimental lesions obtained.

A married woman, aged 41 years, with a history of cholecystitis, of 19 years' duration, with recent exacerbations, was operated on. A cholecystogram had not been made. At operation subacute cholecystitis was found implanted on chronic cholecystitis, and there were multiple stones. Cultures made from the wall of the gall bladder and from the bile contained green-producing streptococci. Cultures of the central portion of the stones were sterile.

Two rabbits were each given intravenous injections, on 2 successive days, of 4 and 5 cubic centimeters, respectively, of a glucose-brain-broth culture of this streptococcus. Six days later, the rabbits were definitely ill and were despatched. One rabbit had empyema of the gall bladder and slight perihepatitis. Sections of the wall of the gall bladder revealed numerous streptococci in places and coexisting coccidium cuniculi infection of the gall bladder. Cultures of the bile contained numerous green-producing streptococci, whereas all other cultures were sterile. There were no gross lesions in the other rabbit except those found in the gall bladder, which was distended and the wall of which was œdematous and thickened, with irregular, white, confluent areas (Fig. 1). Adherent to the mucosa were numerous, tiny, grayish-white, phlebolith-like bodies; there were also a few of these bodies free in the bile, which was watery and pale grayish-green, but which otherwise was grossly unchanged. Cultures of the blood, spleen, and joints were sterile. Those of the bile and wall of the gall bladder consisted of countless green-producing streptococci.

Sections of the wall of the gall bladder (Fig. 2, *a*) showed evidence of destruction of the raised portions of the mucosal folds, with round cell infiltration; many of the cells were leucocytes. Figure 2, *b* shows the streptococci in the necrotic areas shown in Figure 2, *a*.

The following results were obtained with a mixed culture of streptococci and bacillus coli.

A woman, aged 61 years, had been operated on previously for empyema and fistulas of the gall bladder, at which time approximately two-thirds of the gall bladder had been removed. She returned 3 years later with a recurrence of symptoms. At operation, chronic catarrhal cholecystitis was found; the walls of the gall bladder were thickened. Cultures made from wall of the resected gall bladder consisted of a mixture of green-producing streptococci and bacillus coli.

Two rabbits were each given injections, on 2 successive days, of 5 and 6 cubic centimeters, respectively, of a glucose-brain-broth culture of this mixture. One of these rabbits died 63 days later. The body was emaciated, but there were no gross changes except those found in the gall bladder, which consisted of definite empyema with tiny stone-like

Fig. 5. Stones in the gall bladder of a rabbit 44 days after two intravenous injections of 4 and 5 cubic centimeters, respectively, of a 24-hour glucose-brain-broth culture of streptococci and staphylococci obtained from a surgically resected gall bladder.

bodies free in the bile. The other rabbit was despatched, 28 days after the first injection. Necropsy did not reveal gross lesions, except that the gall bladder was distended and the walls were white and thickened (Fig. 3). The bile was replaced by a seropurulent fluid in which were many small, white flakes. Direct smears of this material revealed gram-negative bacilli and streptococci.

Sections of the wall showed it to be markedly thickened and infiltrated throughout with leucocytes; the mucosa was destroyed (Fig. 4, *a*). Figure 4, *b* shows the bacilli and streptococci scattered throughout the necrotic and seminecrotic tissues.

In order to suggest the probable relation of bacteria to formation of gall stones, the following experiment is recorded.

Cultures were made from a surgically resected gall bladder in which subacute, slightly hæmorrhagic cholecystitis was implanted on chronic cholecystitis. There was one fairly large stone in the lumen of the gall bladder. A rabbit was given an intravenous injection on two successive days, with 5 and 4 cubic centimeters, respectively, of a glucose-brain-broth culture of green-producing streptococci and staphylococcus albus obtained from the wall of the surgically resected gall bladders. The rabbit remained apparently well and was despatched 43 days later. Necropsy revealed a distended gall bladder, the wall of which was thickened throughout but was markedly thickened in places so as to form small, sessile nodules 2 to 5 millimeters in their greatest diameter, attached to the tips of the folds of the mucosa (Fig. 5). There were also two such nodules free in the

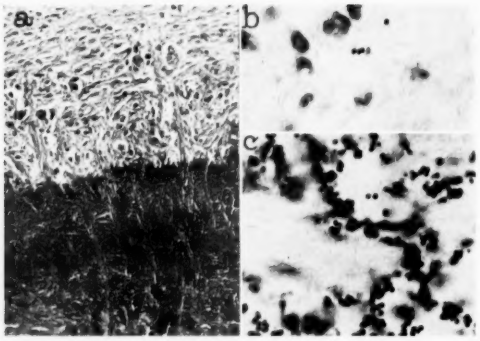

Fig. 6. *a*, Section of the wall of the gall bladder shown in Figure 5 at the juncture of the stone with the villus. Strands of viable connective tissue run for varying distances into the dark necrotic (stone) portion (hæmatoxylin and eosin, ×350); *b*, streptococci in the living part of the villus; *c*, myriads of streptococci and staphylococci in the necrotic (stone) portion of the villus.

bile, which was abnormally viscid and pale grayish-green. Touching and cutting these nodules revealed them to be firm, putty-like masses, containing some gritty or calcareous substance. Cultures of the bile and of portions of these "stones" consisted mainly of green-producing streptococci, with staphylococcus albus.

Sections of the wall through such areas revealed it to be markedly thickened and œdematous. The mucosa was largely necrotic and was absent in places. The nodules were situated at the former site of the tips of the folds of the mucosa which they replaced. There was a sharp line of demarcation between the wall and the nodules. The nodules consisted of a homogeneous, firm, pink mass of eosin-staining material containing myriads of bacteria. In the nodules, near the attachment to the wall of the gall bladder, were strands of apparently viable connective tissue that so far had resisted the action of the bacterial products. These connective tissue strands were continuous with the connective tissue of the wall of the gall bladder (Fig. 6, *a*). The streptococci and staphylococci were most numerous at the distal end of the nodules (Fig. 6, *b*), and they decreased in number as one approached the juncture of the nodule with the wall of the gall bladder. Streptococci also were found for some distance in the grossly unchanged tissue beneath the nodules (Fig. 6, *c*).

These experiments re-emphasize the fact that in certain forms of cholecystitis pathogenic organisms are present, especially green-producing streptococci and gram-negative bacilli. On the contrary, when the pathological diagnosis is "strawberry" gall bladder, cultures from such tissues are usually sterile

unless there are complicating factors such as hepatitis or stones in the ducts.

By classifying the patients according to symptoms, we were better able to determine the relationship of bacteria to cholecystitis. For example, in a patient with a stone in the common bile duct, one would hardly expect to find pathogenic bacteria in the wall of the gall bladder unless it also was diseased or unless the bacteria had entered the gall bladder during stasis of its content. Likewise, one would not expect to find bacteria very frequently in gall bladders from patients in group 3 whose symptoms were not typical of cholecystitis. In some of the patients in group 3 gross evidence of cholecystitis could not be found at operation. Instead, there was found in some cases, hepatitis, duodenal ulcer, or an inflamed appendix, whereas in others various adhesions were found by which the symptoms could readily be explained. In such instances, without gross evidence of cholecystitis, one would not regularly expect to obtain pathogenic bacteria from the wall of the gall bladder.

Patients in group 2 had a rather chronic condition, and unless exacerbations occurred at various times, the chances for obtaining a positive culture here also were minimal. On the other hand, the majority of cultures from patients in group 1 should be positive if bacteria are associated with the cholecystitis, and this seems to have been our experience. The majority of positive cultures containing streptococci especially were obtained from patients in group 1, whereas the majority of sterile cultures were obtained from patients in the other groups. We had hoped that there might prove to be a much longer interval of time between the giving of the dye and the cultures of the wall of the gall bladder in those cases in which the cultures were positive, in contrast to the cases with negative cultures. In accordance with our hopes there was a difference of 2 and 3 days between the cultures that were sterile and those that were positive for the cocci. Perhaps this was sufficient to account for the difference in the cultural results. If so, it may help to explain why cultures of resected gall bladders made recently contained streptococci less often than the cultures obtained 4 or more years ago, such as Rosenow's. It may show, moreover, that the dye is endowed with therapeutic value.

RESULTS OF BACTERIOLOGICAL INVESTIGATION OF SURGICALLY RESECTED GALL BLADDERS

Groups	Symptoms of disease of the gall bladder	Cultures			Predominating organism isolated, per cent		
		Number	Positive	Positive, per cent	Streptococci	Bacilli	Staphylococci
1	Typical, acute	96	64	68	70	16	14
2	Typical, chronic	82	42	51	31	40	29
3	Vague	116	41	35	20	39	41
4	Stone in gall bladder or common bile duct	6	3	50		67	33
	Total	300	150	50	44	30	26

There is another reason why Rosenow's results are higher than ours. His work was done years ago, when surgical measures were postponed until definite disease of the gall bladder was found. Then, too, he worked with selected cases in which gross pathological states of the gall bladder were marked, and he rejected those gall bladders that were grossly unchanged.

That streptococci became localized in a gall bladder previously infected with coccidium cuniculi illustrates that places of lowered resistance may be more susceptible to infection. It does not necessarily vitiate the factor of elective localization, because in many instances streptococci obtained from cases other than those of cholecystitis and injected into rabbits, the gall bladders of which were infected with coccidium cuniculi, did not localize in such previously infected gall bladders but produced lesions elsewhere.

Most of our experimental data in rabbits are in accordance with those of other similar studies. However, the production of cholecystitis with organisms other than streptococci, namely, gram-negative bacilli, is of significance because it implies that these bacilli are not merely secondary invaders, a point originally mentioned by Rosenow. It also strengthens the idea of many that typhoid bacilli, apparently quiescent for a time in the gall bladder, may give rise to disease of

the gall bladder, and that, therefore, the gall bladder may act as a focus of infection. Our inability to produce lesions with pure cultures of staphylococci strengthens the idea that they are relatively unimportant.

At the time of the writing of this paper the report of Branch was noted. His results compare very closely with ours, even as regards the bile in the media. He found the following organisms in cultures and they are listed in the order of their frequency: bacilli, streptococci, and staphylococci. Our results would place the streptococci first and the bacilli second. His conception of the bacterial content in various types of gall bladders is similar to ours and is aptly expressed in the following statement: "As for the relative frequency of the types of cholecystitis from which we recover organisms, the disconcerting consistency of positive cultures from the acute cases is only equalled by the persistent lack of growth from the chronic cases."

CONCLUSIONS

1. The majority of surgically resected gall bladders from patients with acute or subacute cholecystitis contain pathogenic bacteria, whereas the majority from patients who have chronic cholecystitis are sterile. The organisms isolated are, according to their frequency, green-producing streptococci, gram-negative bacilli, and staphylococci.

2. Cultures from "strawberry" gall bladders are usually sterile unless there is a complicating factor.

3. There is a longer time interval between the giving of the tetiothalein sodium-N.N.R. and the making of cultures from the gall bladders in those cases in which the gall bladders were found to be infected than in those that were sterile.

4. Streptococci isolated from grossly diseased gall bladders are of etiological significance, since they tend to reproduce the cholecystitis and cholelithiasis in experimental rabbits when injected intravenously. The colon bacillus also may have a selective action for the gall bladder. It is usually found together with the streptococcus and is found frequently in relatively acute cases or in cases in which there are stones in the common or cystic duct. Staphylococci also are encountered, but we have found them to be nonpathogenic for the gall bladders of rabbits when injected in pure culture.

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PSEUDOTUBERCULOUS SALPINGITIS

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THIS report is concerned with a foreign body type of inflammatory process in the oviduct which simulates tuberculosis histologically and which we believe has frequently been confused with tuberculosis of the oviduct.

Tuberculosis salpingitis, according to current conceptions, constitutes about 10 per cent of chronic adnexal disease. As gauged by statements in commonly recognized reference works on surgery, gynecology, and pathology, it is usually regarded as the common form of genital tuberculosis in the female. Numerous authors state that it is benign in course, in contrast to many forms of surgical tuberculosis, and that following salpingectomy recovery is prompt and permanent in a large share of the cases.

Clinicians have naturally distinguished between cases in which tuberculosis is apparent elsewhere or widespread in the abdomen and those in which it is limited to the tubes. It is quite likely that the favorable course in cases of the latter type is largely responsible for the benign reputation of the disease.

Our attention was attracted to the disease by observation of 3 cases in current pathological material, of large, irregular, ring-like masses of some foreign substance in sections of oviducts, which though much enlarged and patently diseased had some of the gross features of tuberculosis. The histological details in these cases showed clearly that the foreign material was not a residuum of previous caseation. They were generally enclosed in the bodies of large giant cells and there was usually associated a granulomatous reaction with extensive endothelial hyperplasia, tubercle-like focal lesions, and in some instances limited anæmic necrosis. These interesting cases were long the subject of study and from the appearances of the rings of foreign substance it was suggested that they might be the shells of dead parasites, possibly oxyuris vermicularis, as the worms are reported to have been found in the tubes by several observers. Further observations made this explanation of the nature of the substance appear incorrect but also prompted a critical review of the available cases classified as tuberculous salpingitis. Thirty-four specimens containing this foreign material have been found in a total of 78 cases previously diagnosed as tuberculous salpingitis. A review of these specimens made apparent the fact that the foreign material was present in cases in which the lesions were least typically tuberculous and not discoverable in those cases in which there was more satisfactory histological evidence of tuberculosis.

PATHOLOGY

Gross pathology. A review of the operation notes of the surgeons who had cared for the 78 patients showed that the existence of tuberculosis in the pelvis was suspected in only about one-third of the cases on examination of the organs *in situ*. In about the same number of the cases pinhead-size gray bodies were visible on the serous surfaces of the tubes and occasionally on the surfaces of contiguous viscera. Free fluid was present in the pelvis in about one-sixth of the cases and in a few of these it was blood stained. The degree of enlargement of the tubes varied somewhat but they were not usually more than 1.5 to 2 centimeters in diameter. In several cases there was complicating secondary infection with puriform material in pockets between adhesions. Adhesions in the pelvis were usual but did not differ from the adhesions in chronic pelvic disease. They were usually formed by simple, not tuberculocaseous, granulation tissue.

After removal the oviducts were enlarged and firm and tubercle-like bodies were more commonly visible than at operation. On section they were gray or pinkish gray, sometimes with softened centers. In only one-third of the cases was there gross caseation. With but 4 exceptions the tubes on section were of essentially normal shape and the increase in size was due mainly to increase in bulk of the mucous membrane. In a large number of the

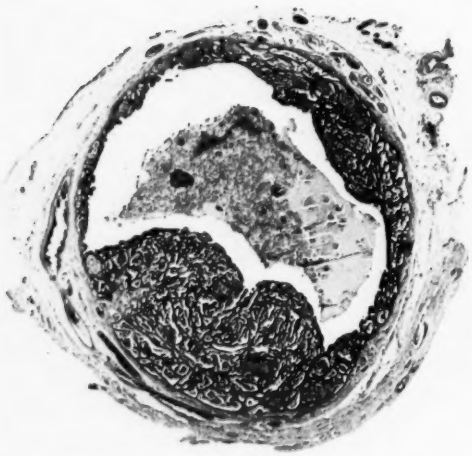

Fig. 1. Cross section of oviduct. The outlines of most of the mucous folds are still visible. The muscle coat is not thickened. The outlines of five or six small foreign body tubercles can just be made out at this magnification.

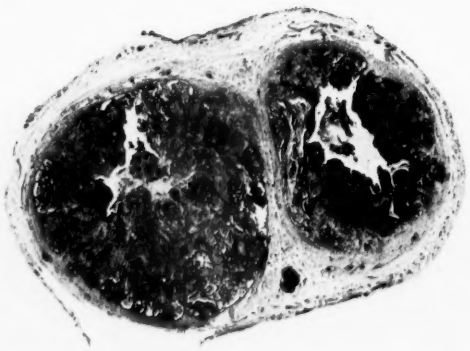

Fig. 2. Cross section through an oviduct bent on itself. There is great increase in thickness of the mucous membrane. The outlines of some mucous folds are visible. There are no lesions in the muscle coat or subserous tissue.

cases the site of the lumen was filled with a solid red core. The ovaries were not usually involved unless incorporated in the adhesions or inflammatory tissue about the tubes. In brief, the tubes on section usually had neither the appearances of a chronic suppurative process nor of frank caseation.

Microscopic pathology. In the 57 cases in which we considered that the morphological changes were deficient in important characteristics of tuberculous lesions, including the 34 cases in which the collections of foreign material were found, the lesions were limited to the serous and mucous coats. The lesions of the serous coats were of two types: small tubercle-like nodules, which formed in or about subserous lymphatics, and simple granulation tissue. Many of the small, gray bodies visible grossly were not tubercles but small collections of lymphoid cells, some even having germinal centers. Most of the subserous nodules were of foreign body tubercle type with a delicate reticulum and numerous small giant cells.

The increase in bulk of the mucous membrane was mainly due to the following basic lesions: focal collections of small giant cells, nodular and diffuse endothelial hyperplasia, fibroblastic reaction on the part of the subepithelial stroma, and proliferative reaction in the epithelium.

The most frequent lesions were the small giant cell and endothelial nodules. They formed in the substance of the folds of mucous membrane either near the tips or down close to the internal muscle layers. While they produced some distortion of the mucous membrane, the general outlines of the mucous folds were generally fairly well retained. Particles of foreign material have been found in approximately half of these nodules.

Fibroblastic proliferation was extensive in some cases and either limited to the peripheral portions of nodular lesions or more diffuse. It was usually accompanied by endothelial proliferation and infiltration by lymphocytes.

Epithelial proliferation was extensive in some cases. If marked, the projections of the mucous membrane were broad and bulbous and covered with several layers of epithelium. There was a tendency to fusion of mucous folds with the formation of irregular, epithelial lined canals or islets of atypical epithelium.

In some specimens there was limited, central softening. This was usually associated with excessive mucous secretion, not only into the lumen and epithelium-lined canals but also into the stroma of the mucous membrane. There was often scanty hæmorrhage. As a consequence the lumina were often filled with a mixture of mucus, red corpuscle and epithelial cell débris.

Fig. 3. Foreign body tubercles in distorted mucous folds. The giant cells contain crystalline material.

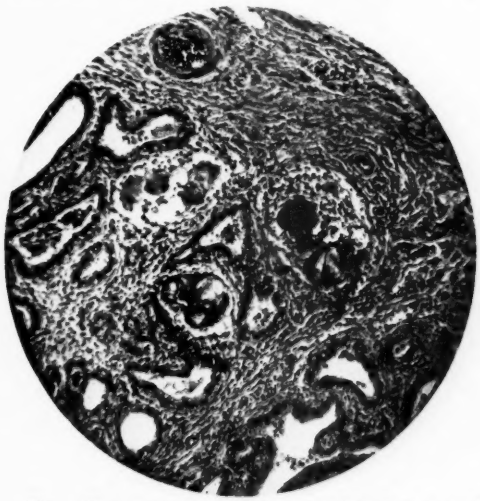

Fig. 4. Two masses of foreign material in the bases of mucous folds. The foreign body tubercle at the left contains material in the form of fine particles.

DIFFERENTIATION FROM TUBERCULOSIS

Through the courtesy of Dr. Douglas Symmers, director of laboratories at Bellevue Hospital, we have had the opportunity of comparing the lesions in this surgical material with those in 10 autopsies in cases of disseminated tuberculosis in which the oviducts were involved. In the autopsy specimens the tubes were larger, they could not usually be separated from the tuberculous granulation tissue about them, caseation was extensive and usually extended into and through the muscle coats, and the tubercles on the surfaces were frequently confluent and caseous.

In the surgical cases none of the recent accessions have had typical tuberculous lesions, and it therefore happens that the 14 cases in which there was reserve material for the application of stains for tubercle bacilli have been among those which we regard as pseudotuberculous. We have been unable to find tubercle bacilli in these and although failure to demonstrate tubercle bacilli has only negative value, it is pertinent to state that the lesions in these cases were not of such type as to suggest the presence of acid fast or other bacteria.

CLINICAL ASPECTS

An analysis of the clinical records of the total series of cases has been made, and there appear to have been consequential differences in the clinical manifestations in the 21 cases in which the lesions are comparable to the lesions in the postmortem material reviewed and those in which we are inclined to believe the lesions are of foreign body type. The patients gave more evidence of being seriously ill. In 9 cases there was adequate evidence

Fig. 5. Larger foreign body tubercles. Additional foreign substance visible with polarized light.

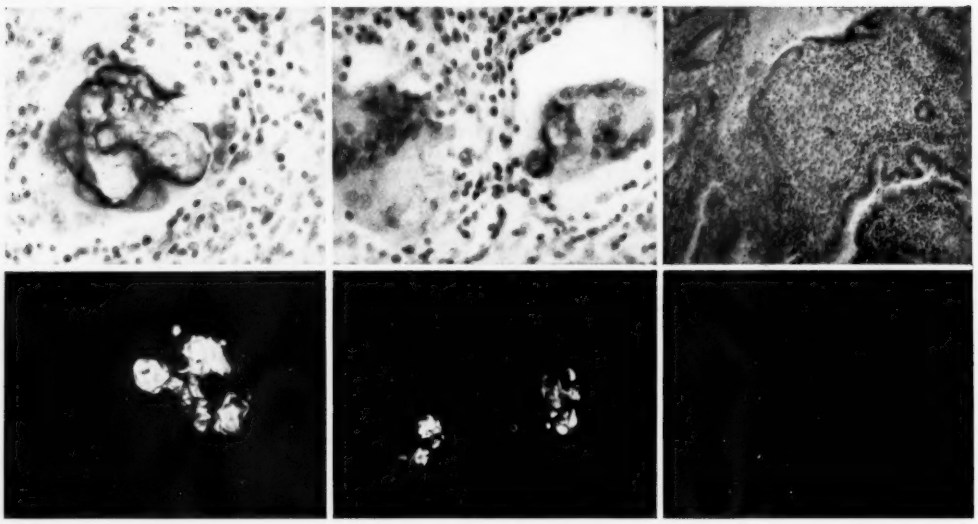

Fig. 6. The foreign material in identical fields when examined with natural and polarized light.

that there was tuberculosis in other organs. Three had definite signs of pulmonary tuberculosis. Two of these died within a year of tuberculosis. Two had extensive tuberculosis of the peritoneum and chronic, obdurate sinuses persisted after operation. One patient had previously had a tuberculous kidney removed. She died a little more than a year after operation. In 3 cases there were definite lesions in the endometrium. In the 12 remaining cases in which the histological evidence of tuberculosis appeared sufficient the subsequent course of the disease is not satisfactorily known.

In the larger group in which we regard the histological evidence of tuberculosis as inconclusive or inadequate, the presenting symptoms were decidedly less severe. They generally sought relief from a troublesome, but not alarming, condition in the lower abdomen or pelvis. A presumptive diagnosis of genital tuberculosis was not made in any of the cases before operation, and in many cases the oviducts were not suspected of being the site of the trouble. The patients were, practically without exception, described as being well nourished and in fair to good general health. In several instances the diseased oviducts were discovered in the course of operations for other gynecological conditions, as myomata uteri, ovarian cysts, uterine cancer, etc. Our information as to the eventual outcome of these cases is extremely meager. The immediate outcome was favorable with but one exception and in this case the patient died as the result of a surgical accident.

THE NATURE OF THE FOREIGN MATERIAL

After the group of cases in which the histological evidence of tuberculosis appears adequate is set aside, the tuberculous nature of the process in the remaining cases in which the foreign material was and was not found seems about equally uncertain. Since the foreign material appears to be responsible for the formation of the giant cells in many cases, considerable interest attaches to its nature.

When examined with natural light in stained preparations the substance most readily visible is that forming the irregular basic-staining rings. These masses vary in size from 15 or 20 micra up to collections 60 to 80 micra in diameter. When hæmatoxylin has been briefly applied they may fail to stain and appear yellowish-brown and slightly refractive. The material consistently gives a strongly positive von Kossa's reaction for calcium. They fail to react to this reagent

after brief treatment with weak acids, hydrochloric and nitric, or with acid salts, as copper acetate. They are fast to fat solvents, hot alcohol, ether, and xylol. After treatment with acids they are still stainable with ordinary histological dyes. Calcium sulphate crystals can be observed in formation microscopically when sulphuric acid is drawn under the cover slip.

Examination with polarized light gives additional information as to the amount and nature of the material. When observed with crossed Nicol prisms, great numbers of refractive, crystalloid clusters become visible in the centers of the basophilic masses and in the bodies of giant cells and endothelial nodules. All the material appears to be anisotropic. The individual crystals vary greatly in shape, many forms probably being abortive or imperfect crystal formations. The crystalline material is partially soluble in acids, forms calcium sulphate crystals, and does not form gas bubbles when treated with hydrochloric acid. It does not reduce silver nitrate (von Kossa's reaction), probably on account of its relative insolubility.

Several unstained preparations were referred to Dr. Emil M. Chamot, professor of microscopic chemistry at Cornell University. He was able to extract the material from the preparations and to identify calcium phosphate and considerable amounts of ammonium magnesium phosphate. He suspected small amounts of calcium oxalate but was unable to assure himself on this point.

The more minute deposits in the nodules of endothelial hyperplasia are too small to permit of isolation and identification, but it appears likely that they are of similar composition and that the three forms in which the material is visible represent accretion stages.

Since it has taken many years for this considerable number of cases to accumulate fresh tissues for the application of fat stains have not been available. In several cases the cover glasses of frozen section preparations were soaked off and in this way small amounts of amorphous and crystalline fatty acids have been identified. This finding suggests that the ring-formed bodies have their origin in deposition of fatty acids, saponification, and calcium absorption. It is clear that further observations with fresh tissue are necessary in this connection.

THE SIGNIFICANCE OF THE FOREIGN MATERIAL

Our studies convince us that the peculiar lesions in the oviducts in nearly half of the cases are caused by the formation of foreign bodies in the tissues. We are certain, from reading the reports of the pathologists by whom the diagnoses of tuberculous salpingitis were made, that they were all greatly influenced in their decisions that the lesions were tuberculous by the presence of the giant cells. The view that this foreign substance is not a natural product of a tuberculous inflammatory process is supported by the fact that it is absent in the more typically tuberculous lesions. Calcium and magnesium phosphate are natural products of tissue and tissue juices but their presence in crystalline form in so many similar lesions requires explanation. Possibly in the course of an inflammatory reaction in the oviduct pathological metabolites, in the form of crystalline material, persist as foreign bodies and cause lesions simulating those of tuberculosis. This view certainly offers some explanation of the benign character of the disease.

SUMMARY

In a strict sense we have presented no conclusive evidence that the reaction in these cases is not a peculiar reaction to the tubercle bacillus. The absence of definite tuberculous granulation tissue, an obvious alternative cause for the formation of the giant cells, and finally, the lack of any clinical evidence of tuberculosis in other organs are cogent reasons in favor of our contention. It is clear that the problem requires further investigation. There are numerous instances in pathology in which it has been necessary to separate pseudotuberculosis from genuine tuberculosis, as in the mammary gland, thyroid, ischiorectal tissue, etc. At least, it is reasonable to insist that suspected cases of tuberculous salpingitis should be subjected to rigid bacteriological tests and that personal opinion as to the nature of histological lesions should be supported by animal inoculations.

SOLITARY CYSTS OF THE KIDNEY

A Report of Seven Cases and Observations on the Pathogenesis of These Cysts[1]

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IN no other phase of renal pathology has there been so much fascinating speculation as to etiology, uncertainty as to pathogenesis, and lack of adequate classification as in the so-called solitary cysts of the kidneys. The term "solitary" has been used to distinguish the large cysts of adult life from congenital polycystic kidneys and from the multiple small retention cysts of chronic nephritis. Yet the assumption that these cysts are an entity with a common origin on the basis of number and size alone does not seem justified from a review of the reported cases.

Many cysts have been recorded under the title of solitary that vary widely in their pathological features. Although they are defined as voluminous cysts, occurring singly in a kidney otherwise normal, a review of the cases which have appeared in the literature under this generic term shows that in many instances they were multiple and in some bilateral; that a large number were associated with definite and marked pathological conditions in the same kidney; and that many were indistinguishable from the larger nephritic cysts. Quite frequently hæmorrhagic cysts have been included in the tabulation of solitary serous cysts.

From a study of the reported cases it is evident that this lack of conciseness is caused by the fact that large cysts in the kidney are not a distinct entity with a common histogenesis but that their direct etiology varies and because of this they may differ as to number, size, contents, sac wall, and associated renal pathology. It is my contention, however, that the mechanism of their production is essentially the same.

The same confusion exists in the classification of hæmorrhagic cysts. Leopold suggested that they are a result of bleeding into a serous cyst. Some of them are. But there is a great difference between the thin walled cyst with serosanguinous contents, which evidently arise on this basis, and those whose thick walls contain large amounts of fibrous tissue, atrophic renal parenchyma, at times remnants of tumor tissue, and an inner layer of organized blood clot arranged in superimposed lamellæ of various ages. It has been suggested that they arise from hæmorrhagic infarcts or encapsulated hæmatomata. Others contend that all these hæmorrhagic cysts develop in neoplasms which have been destroyed in the growth of the cyst and the cells of which are left as remnants in the sac wall. Judd and Simon reported two cysts which they felt had their origin in aneurisms because of elastic tissue, intima, and endothelium in the wall. They feel that this is the most likely cause of hæmorrhagic cysts.

So we find that there is a tendency for each author to describe the origin of this condition on the basis of his own particular case, being careful to exclude from his classification others with a definite etiology and with slight pathological differences, and losing sight of the fact that these cysts may not be a distinct entity with a common origin. The direct cause may vary and with it the pathological features, but the mechanism of the cyst formation is essentially the same.

The object of this paper is to report 7 cases of large solitary cysts of the kidney, 4 serous and 3 hæmorrhagic, to present a review of the reported cases with particular reference to the etiology, and to describe the experimental reproduction of a solitary cyst which substantiated a new conception of their pathogenesis.

REVIEW OF THE REPORTED CASES

I have been able to collect 249 cases, 212 of which were large serous cysts and 37 hæmorrhagic (Table I). Seven personal cases, 4 serous and 3 hæmorrhagic, bring the total to 216 serous and 40 hæmorrhagic. Cunningham's 29 cases of small solitary cysts associated with nephritis from the autopsy records of the Boston City and Long Island Hospitals are not included in this study.

[1] Read before the Clinical Society of Genito-Urinary Surgeons, San Francisco, July 15, 1929; also Chairman's address: Symposium on Surgery of Kidneys and Bladder, Pan-Pacific Surgical Congress, Honolulu, T. H., August 23, 1929.

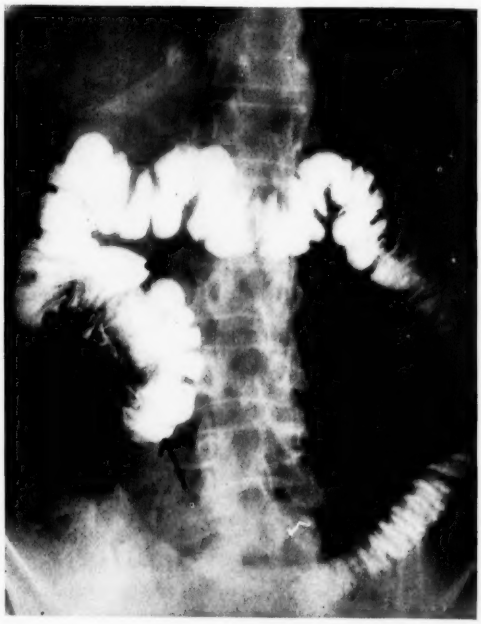

Fig. 1. Roentgenogram of barium enema showing displacement of cæcum and ascending colon by large cyst of right kidney. (Case 1.)

Fig. 2. Pyelogram showing deformity produced by large cyst of right kidney. (Case 1.)

The difference in the number of collected cases of hæmorrhagic cysts in this report and in that of Judd is caused partly by the fact that he excluded all cases associated with tumor and partly because quite a few cases of simple hæmorrhagic cysts have not been reported under that title but have been included in tabulations of simple serous cysts.

The increasing number of case reports of solitary cysts indicates that this condition is not as rare as was formerly supposed. This opinion is held by Branch (189), who says that, although they are comparatively rare clinically, because many of them do not grow sufficiently large to cause symptoms, they are not a rarity to the pathologist and occur in 3 to 5 per cent of all autopsies.

A careful review of each case in which data was available has brought out the following pertinent facts with particular reference to etiology (Table II). The average age incidence for the serous was 45, for the hæmorrhagic 48 years. Females were affected about twice as frequently as males.

In many instances a comprehensive clinical history was not given. When it was, it is of some significance that in quite a few the onset

TABLE I.—REPORTS OF COLLECTED CASES OF SOLITARY CYSTS OF THE KIDNEY

Serous cysts	Collected	Personal	Total
J. Simon, 1906	52	..	52
Kretschmer, 1920	99	1	100
Harpster, 1923	95	2	97
McKim and Smith, 1924	117	3	120
Laquiere, 1925	119	5	124
Clark M. Johnson, 1926*	135	2	137
E. Dozsa, 1927	127	3	130
Carson, 1928	147	4	151
Present report	212	4	216
Hæmorrhagic cysts			
Souligoux and Gouget, 1905	7	1	8
Judd and Simon, 1927	13	2	15
Manna	18	1	19
Present report	37	3	40

*Personal Communication.

TABLE II.—CLINICAL DATA

	Serous	Hæmorrhagic	Total
Average age	45	48	..
Sudden onset of symptoms followed shortly by appearance of a mass	15	3	18
Average duration of symptoms in years	..	..	2½
Rapid growth of cyst	18	8	26
Sex			
Females	..	..	163
Males	..	..	79

Fig. 3. Drawing of large, thick walled, solitary cyst of right kidney. (Case 1.)

of symptoms was sudden and the growth of the cyst rapid. The average duration of symptoms was 2½ years. In 26 cases there was a rapid increase in the size of the cyst over a period of a few weeks to months.

In 30 instances, the cysts were multiple and in 9 bilateral (Table III). The sac wall was invariably composed of fibrous, connective tissue of different degrees of thickness in both the serous and the hæmorrhagic.

In 25 cases, there were remnants of renal parenchyma, atrophic tubules, and glomeruli in the wall, not only at the cyst's point of contact with the kidney but in all portions of the sac. This indicates that in these instances the wall was made up of compressed renal parenchyma with a connective tissue substitution which was not complete. In addition, many of the hæmorrhagic cysts had an inner layer of clot and fibrin.

TABLE III.—PATHOLOGICAL DATA

	Serous	Hæmorrhagic	Total
Multiple (2 to 5)	25	5	30
Bilateral	6	3	9
Sal wall			
Remnants of renal parenchyma. Atrophic tubules and glomeruli	16	9	25
Tumor—adenocarcinoma, hypernephroma, angioma	..	10	10
Calcification	4	5	9
Muscle and elastic fibers with remnants of intima	..	2	2

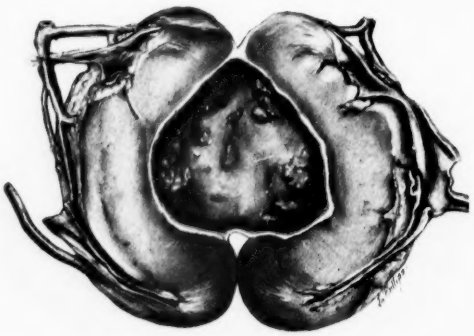

Fig. 4. Drawing of sagittal section of kidney. (Case 1.) There is a reversal of the kidney form. The internal border is convex and the external concave. Note the anomalous blood vessels and distortion of the pelvis.

In 10 of the hæmorrhagic cases there were small irregular strands of tumor tissue scattered throughout the wall. These cases must not be confused with the ordinary cystic degeneration of tumors. When this occurs there is a predominantly solid tumor containing numerous large and small cyst-like cavities. Here we refer to the large monolocular cysts with no gross evidence of tumor except, perhaps, a small nodule at the deepest point of the cyst's contact with the kidney and remnants in the sac wall.

Two cases were reported in which the wall contained muscle fiber, elastic fibers, and remnants of intima, from which it was concluded that the cysts arose from aneurisms. In 9 cases there was definite calcification.

TABLE IV.—ASSOCIATED LESIONS IN THE SAME KIDNEY

	Serous	Hæmorrhagic	Total
Chronic nephritis—diffuse or interstitial	18	1	..
arteriosclerotic	10	2	31
Tumor—hypernephroma, angioma, adenocarcinoma	3	12	15
Anomalies			
Horseshoe	5	..	..
Dystopia	2	..	9
Double pelvis	2	..	..
Calculi	10	..	10
Anomalous arterial supply	3	1	4
Hydronephrosis	4	..	4
Pyonephrosis	2	..	2
Infarct	3	..	3
Leukæmic infarct	1	..	1
Tuberculosis	1	..	1
Possible aneurism—branch renal artery	..	2	2
	64	18	82

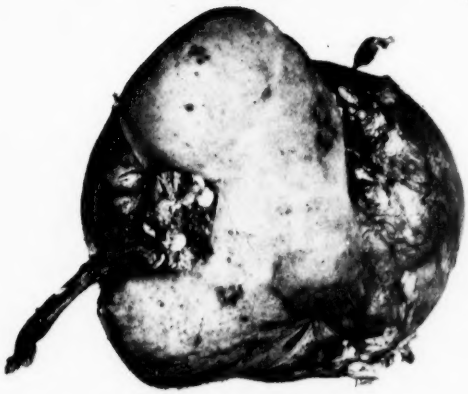

Fig. 5. Large, solitary, hæmorrhagic cyst arising from the lower pole of the left kidney. (Case 2.)

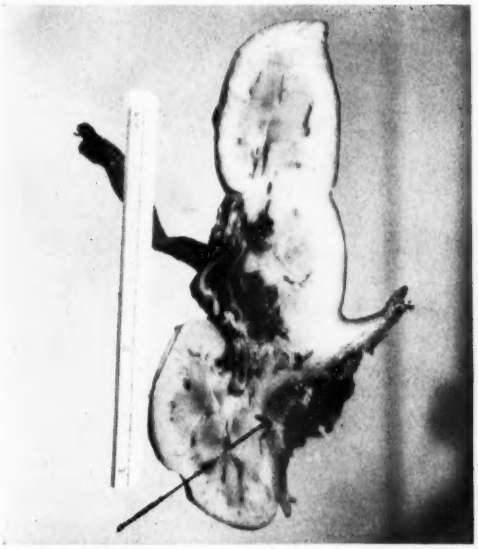

Fig. 6. Kidney after removal of the cyst showing its point of attachment to the lower pole and the small nodule of tumor tissue at this point. (Case 2.)

Although solitary cysts are defined as occurring in a kidney otherwise normal, in 82 instances there was definite renal pathology in the same kidney (Table IV). This is a higher percentage than the figure indicates because of the frequent lack of any pathological report and of careful histological study of the kidney. It will be noted that chronic nephritis was present 31 times. This does not include the degenerative and sclerotic changes in the vicinity of the cyst which have been attributed to pressure. In 12 instances the kidney was definitely arteriosclerotic. In 3 the cyst arose from an infarct. Eighteen of the hæmorrhagic cysts were associated with other conditions, 12 of which were tumors.

Case 1. A woman, aged 50 years, was admitted to the Seattle City Hospital, February 28, 1926, complaining of pain and soreness in the lower right quadrant of the abdomen. This had come on suddenly 2 days previously and was accompanied with nausea, vomiting, and diarrhœa.

The temperature on admission was 100 degrees F. There was no leucocytosis and the urine was normal except for a 0.7 per cent sugar and large amounts of acetone and diacetic acid. The blood sugar was 133 milligrams per 100 cubic centimeters.

Examination showed a mass in the lower, right abdominal quadrant, freely movable, not tender, and with no overlying muscular rigidity. A diagnosis was made of fibromyoma of the uterus, diverticulitis of the colon, and diabetes. The last condition was treated by diet and insulin and the patient's general condition improved.

On April 3, patient was referred to the urological service. The renal function, as measured by phthalein, was 60 per cent the first hour and 10 per cent the second. The urine was normal except for sugar, acetone, and diacetic acid. Plain X-ray pictures showed a faint, irregular shadow about the size of a grape fruit in the right lumbar region, just above the iliac crest, and after a barium enema a sharp displacement of the cæcum and ascending colon inward and upward as if by a large, retroperitoneal tumor (Fig. 1).

On cystoscopic examination nothing abnormal was found in the lower urinary tract. The ureters were catheterized with no obstruction and the urines from both sides were normal. The function of the right was one-half that of the left. Pyelo-ureterograms showed a marked deformity on the right, characteristic of tumor (Fig. 2). A tentative diagnosis was made of, first, hypernephroma; second, monocystic kidney.

Operation, April 5, 1926. Because of the possibility of hypernephroma, Cabot's incision (transverse lumbo-abdominal meeting a vertical mid-rectus) was used and the right kidney exposed extraperitoneally. The perirenal veins were markedly dilated. There was a large thick walled cyst on the external border, and because of the impossibility of a resection, a nephrectomy was done. The patient's recovery was uneventful.

Pathological report. The right kidney was enlarged and elongated and the external border replaced by a large thick walled cyst (Fig. 3). There was a reversal of the usual shape of the kidney, the internal border being convex with a resulting distortion of

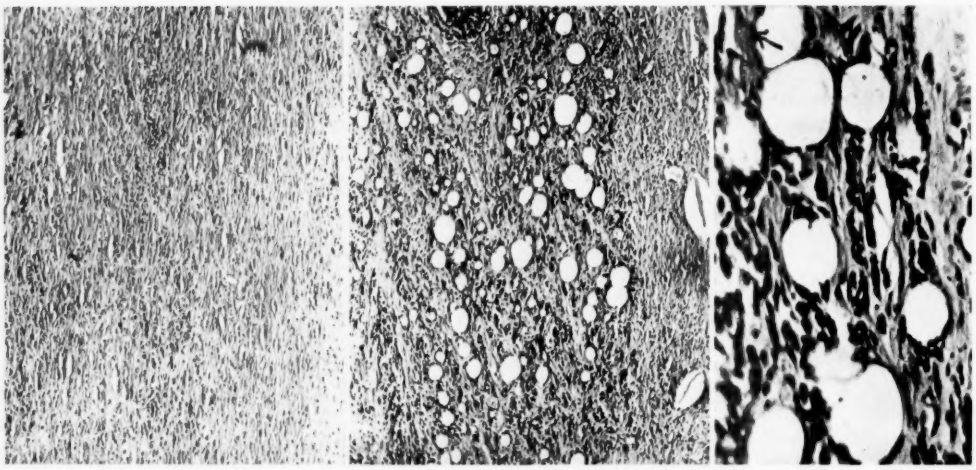

Fig. 7. Fig. 8. Fig. 9.

Fig. 7. Photomicrograph of cyst wall showing complete connective tissue substitution. (Case 2.)

Fig. 8. Low power photomicrograph of dilated, atrophic renal tubules in the cyst wall. (Case 2.)

Fig. 9. High power photomicrograph of the tubules in the cyst wall showing the compressed, atrophic, tubular epithelium structure. (Case 2.)

the pelvis. The blood supply was abnormal (Fig. 4). The cyst had extremely dense, thick walls with areas of calcification, and contained a thick, grumous material. Microscopically, section from the wall showed dense, fibrous connective tissue with occasional areas of calcification. Section from the kidney showed a patchy atrophy and sclerosis with atherosclerosis of the larger vessels, characteristic of the atherosclerotic kidney of Ziegler.

CASE 2. A woman, aged 36 years, a patient of Dr. Homer Dudley, was admitted to the Swedish Hospital, November 16, 1925, complaining of a dull, aching pain and a mass in the left side of abdomen.

In the spring of 1922 she had had an attack of painful urination with frequency and burning. This was followed by a dull, aching pain in the left lumbar region accentuated by walking and by lying on the left side. One month later, there was a painless hæmaturia followed by chills and fever and some pain in the left loin.

Examination by physician showed blood and pus in the urine. A plain X-ray picture was "negative for tumor or stone in the kidney." After 2 months all the symptoms disappeared until 2 years later, when the dull ache in the back returned. This gradually increased until 1 year later the patient noticed a lump in the left side. There was no nausea or vomiting, but some slight dysuria. The physical findings were essentially negative except for a large, symmetrical, freely movable, firm, painless mass in the left abdomen extending from beneath the border of the twelfth rib to the level of the crest of the ilium. The urine showed a trace of albumin, many pus and red blood cells, and bacteria.

Cystoscopy showed a normal bladder, many pus cells in the left kidney urine as compared to a few in the right, and a zero phthalein in 25 minutes from the left as compared to a 25 per cent output in the same time from the right. The left pyelogram showed a slight distortion of the lower calyces but there was a large, rounded shadow of the same density as the kidney shadow and apparently connected with the lower one-half of the kidney. A diagnosis was made of solitary cyst of the kidney and pyelonephritis.

Operation, January 13, 1926. The left kidney was exposed through a left, lumbar oblique incision. A large, thick walled cyst arose from the lower pole. It was firmly adherent to the surrounding tissue. A nephrectomy was done without rupture of the cyst. The specimen (Fig. 5) consisted of a flattened kidney, arising from the lower pole of which was a thick walled cyst about the size of a grape fruit. Its contents were hæmorrhagic. The inner surface was roughened from attached fibrin and small masses of old blood clot. The cyst arose from the medulla near the tip of a pyramid (Fig. 6). At its deepest point of attachment, was a small mass of yellowish, friable tissue, which microscopically proved to be hypernephroma. The kidney tissue immediately surrounding the cyst showed some atrophic changes. The cyst wall was one-quarter centimeter thick and made up of fibrous, connective tissue with some round cell infiltration (Fig. 7). There were areas containing atrophic, dilated renal tubules (Figs. 8 and 9) and several atrophic glomeruli. Scattered throughout the wall were small masses of hypernephroma cells in strands between the fibrous, con-

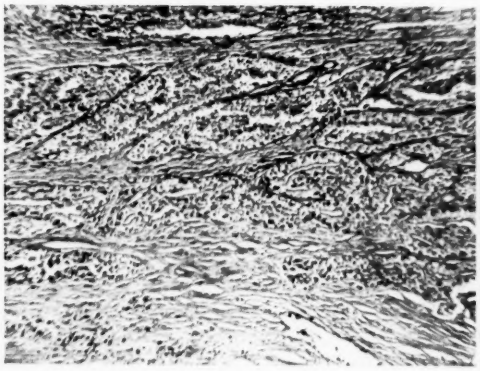

Fig. 10 (left). Strands of tumor tissue such as were found in numerous areas in the cyst wall (low power photomicrograph). (Case 2.)

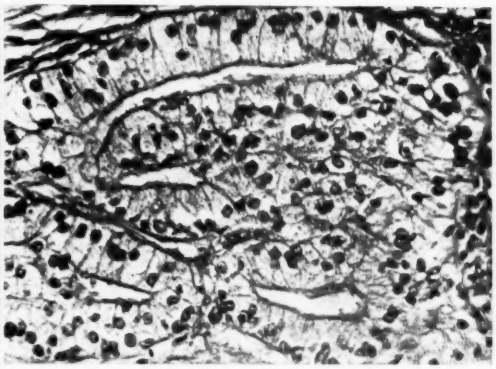

Fig. 11. High power of tumor tissue in the cyst wall showing the cellular arrangement typical of hypernephroma. (Case 2.)

nective tissue (Figs. 10 and 11). The cyst had no epithelial lining.

It is interesting to note that there was nothing in the gross specimen to suggest the presence of hypernephroma. The cyst was indistinguishable from any large, simple cyst. The presence of hypernephroma was demonstrated only after careful microscopic examination of the cyst wall.

CASE 3. A man, aged 60 years, a patient of Dr. R. Mosiman, was admitted to the Seattle General Hospital, February 28, 1927, complaining of hæmaturia and a large mass in the right side of the abdomen. For the past 2 years there had been a painless hæmaturia. Just recently he noticed a mass in the right side of the abdomen, which increased in size. It was not tender and there was no lumbar pain.

The examination showed nothing of importance except a large, smooth mass in the right side of the abdomen extending from the inferior costal margin to the iliac crest. It moved on respiration and was not tender. On bimanual palpation it gave the definite impression of a kidney tumor. The urine contained a trace of albumin, a few pus cells, and a few hyaline and granular casts. A diagnosis was made of hypernephroma.

Operation, March 1, 1927. Because of the enormous size of the tumor, the kidney was exposed transperitoneally. A large cyst almost completely replaced the right kidney. The remaining parenchyma was elongated and spread out over the external border of the cyst. There was a marked enlargement and engorgement of the venous collaterals. A nephrectomy was done without opening the cyst. The patient was alive and well 1 year after operation.

The specimen showed a large cyst 15 centimeters in diameter over the outer side of which were stretched the remains of the kidney measuring 7 by 4 by 3 centimeters (Fig. 12). The contents were hæmorrhagic. At the middle point of the cyst's attachment to the kidney was a yellowish nodule of tumor tissue, which on microscopic section proved to be an adenocarcinoma (Fig. 13). The parenchyma in the vicinity of the cyst showed atrophic changes. The cyst wall was thin and showed a complete connective tissue replacement (Fig. 14). In numerous areas in the wall small strands of tumor tissue were found with the cellular arrangement of an adenocarcinoma (Fig. 15).

Here again as in Case 2 we find a large, solitary cyst with remnants of tumor in the walls but indistinguishable on gross inspection from the simple, large hæmorrhagic cysts not associated with tumors.

CASE 4. A woman, aged 58 years, a patient of Dr. W. Lippincott, was admitted to the Seattle General Hospital, December 13, 1926, complaining of diarrhœa of 2 months' duration. Three weeks ago there was a sharp, colic-like pain in the lower left abdominal quadrant, associated with nausea and vomiting.

The general examination was essentially negative except for a firm, smooth, freely movable mass in the left, upper quadrant. There was no rigidity or tenderness. The blood and urine were normal.

Cystoscopy showed the lower tract to be normal. The ureters were catheterized with no difficulty and the separate urines were normal and the divided functions equal and good. Control X-ray plates showed a shadow the size of a large orange, continuous with the left kidney shadow. Pyelograms showed the left pelvis to be slightly enlarged. The

Fig. 12. Large, solitary, hæmorrhagic cyst of right kidney. Note the nodule of tumor tissue at the deepest point of the cyst's contact with the kidney. (Case 3.)

lower major calyx was flattened, and the entire pelvis pushed upward and inward. A diagnosis was made of simple cyst of the left kidney.

On February 11, 1927, a transperitoneal, left nephrectomy was done through a rectus incision. A large cyst was attached to the lower one-half of the internal border. It was impossible to excise it because of its intimate association with the renal pedicle (Fig. 16).

The specimen showed a kidney 9 by 5 by 4.5 centimeters to the inner border of which was attached a thin walled cyst, 7 by 5 by 6 centimeters, with serous contents. The cut surface of the kidney appeared normal. Microscopic section showed considerable œdema and tubular degeneration. The cyst wall was thin and made up of fibrous, connective tissue with some round cell infiltration.

CASE 5. A woman, aged 59 years, referred by Dr. M. W. McKinney, was admitted to the Seattle General Hospital, April 18, 1926, complaining of a dull pain and tenderness in the right, upper abdominal quadrant with occasional attacks of nausea and vomiting. These attacks started 10 years ago and occurred about every 3 to 4 months.

The general examination was essentially negative except for marked tenderness below the right inferior costal margin. The urine was normal. There was a leucocytosis of 19,400 with 89 per cent polynuclears.

A diagnosis was made of cholelithiasis and an exploratory laparotomy done April 19, 1926. The gall bladder was found to be normal. There was a cyst, the size of a large lemon, attached to the lower pole of the right kidney. A transperitoneal nephrectomy was done. There was an anuria and the patient died of uræmia on the seventh postoperative day.

The specimen was a kidney 10 by 5 by 4 centimeters, attached to the lower pole of which was a thin walled, serous cyst 5 by 3. The walls showed a complete connective tissue replacement. There was no epithelial lining. The kidney showed atherosclerotic changes with glomerular obliteration, scar tissue, and endarteritis in some areas.

CASE 6. A man, aged 66 years, was admitted to the King County Hospital, March 3, 1929, with third degree burns of both legs and feet. He developed a severe infection and toxæmia and died April 16, 1929.

Autopsy report. Chronic myofibrosis, parenchymatous degeneration, arteriosclerosis. The left kidney had a large, solitary serous cyst 7.5 by 5 by 6 centimeters on the middle of the external border (Figs. 17 and 18).

CASE 7. A man, aged 64 years, was admitted to the King County Hospital, August 8, 1928, complaining of a pain in the epigastrium. A diagnosis was made of carcinoma of the prostate, renal calculus, and chronic nephritis. The urine showed albumin, red blood cells, casts, and 10 to 12 pus cells to the high dry field. The phenolsulphonephthalein was 20 per cent in 2 hours and 1 month later 10 per cent in 2 hours. The urea nitrogen was 88 milligrams per 100 cubic centimeters and the creatinin 4.8 milligrams per 100 cubic centimeters. He died of uræmia September 17, 1928.

The clinical diagnosis was confirmed at autopsy. In addition a large, serous cyst associated with several smaller ones was found in an arteriosclerotic left kidney (Fig. 19). It is the same sort of cyst that has frequently been reported under the title of solitary cyst. Yet it is unquestionably a nephritic cyst in an arterosclerotic kidney. In size, gross appearance, and histologically it resembles in every detail the cyst shown in Figure 17 and differs from it only in that the etiology here is evident; in Case 6 it is not. It does not seem reasonable to exclude it from classification under the generic term, solitary cyst, simply because we know its origin.

THEORIES OF ETIOLOGY

Numerous explanations of the origin of these cysts have been given (36 and 200). In the more recent literature, opinions are divided between the congenital theory and the idea that they are acquired, retention cysts. The work of Kampmier (196) and of Reinhoff (199) on the embryology of the uriniferous tubules is quoted in support of the contention that they develop from embryonic rests, persistent cystic tubules in the embryo, or from the failure of union of the glomeruli and tu-

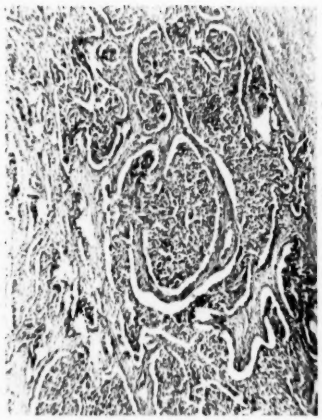

Fig. 13.

Fig. 13. Photomicrograph of tumor nodule noted in Figure 12 showing the structure of an adenocarcinoma. (Case 3.)

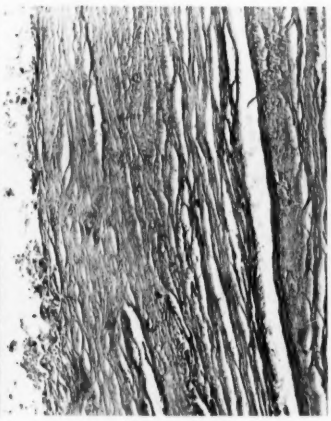

Fig. 14.

Fig. 14. The fibrous cyst wall. (Case 3.)

Fig. 15.

Fig. 15. Cyst wall with small area of tumor tissue of same structure as that noted in Figure 13. (Case 3.)

bules and that they are genetically related to polycystic kidney.

There are various discrepancies in this theory. The disease is one of late adult life, the average age incidence being 45, and it is frequently found in the sixth and seventh decades. It is contended by supporters of the congenital theory that the cysts are slow growing and are not of sufficient size to cause symptoms until middle life; yet in a large percentage of cases considering the absence of clinical history in many the very rapid growth of the cyst over a period of a few weeks or months has been noted. It is not unusual to find a history as follows:

A sudden onset of symptoms referable to the kidney followed by a period of quiescence for a few months, a return of the symptoms, and the appearance of a small mass which increases rapidly in size. For example, in one case a cyst the size of a cricket ball was palpated and in 9 months it completely filled the abdomen. In another a cyst the size of a grapefruit increased to that of a full term pregnancy in 2 months. In another a movable kidney of normal outline was palpated. Three months later there was a cyst three or four times the size of the kidney.

This idea of the rapid growth of these cysts is contrary to the generally accepted opinion although Braasch (108) has referred to it. He states: "The rapidity with which these cysts grow is interesting. Patients not infrequently claim that they have noticed that the tumor which may be the size of an orange or larger, has appeared and grown to its present size within a few months. The etiology has not been determined and would make an interesting problem for someone."

In children these cysts are rare, both clinically and at autopsy. It is hard to reconcile these facts, that is, the age incidence of 45, the rarity in children at autopsy, the sudden onset of symptoms, and, in many instances, the comparative rapidity of growth, with a theory which assumes that they start in early life, grow slowly, and therefore do not manifest themselves until the fourth or fifth decade. It would seem more reasonable to suppose that they were related in some way to the acquired renal lesions which are more common in middle life.

Many investigators support the theory that they are retention cysts and are due to some undiscoverable obstruction in the tubules with active renal secretion continuing distal to the lesion. The commonest obstruction is assumed to be a localized inflammation with peritubular sclerosis and contraction. This is, of course, recognized as the origin of the small, retention cysts of nephritis, but it is considered inadequate by many as an explana-

Fig. 16. Simple, serous cyst of left kidney encroaching on the hilus and renal pedicle. (Case 4.)

tion of these larger cysts. Apparent discrepancies have been: first, that there is no evidence of any obstructive factor in many cases; second, that pathological lesions so situated as to block large groups of tubules are common, yet solitary cysts are comparatively rare; third, that obstruction to the tubules at the papilla has been produced experimentally, and that although there was dilatation, which in some instances persisted, no definite cysts were produced. In other words, group tubular obstruction alone cannot cause these enormous dilatations, which might be compared to

Fig. 18. Section of cyst showing the loss of kidney substance in its formation. (Case 6.)

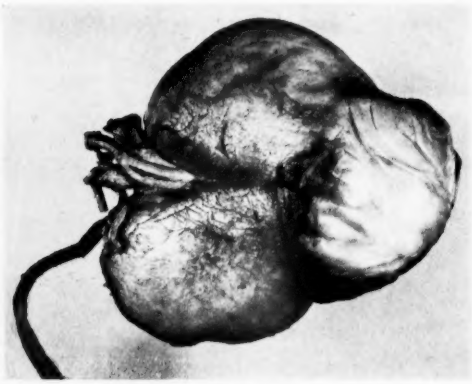

Fig. 17. Solitary, serous cyst of left kidney. (Case 6.)

blowouts of the parenchyma. There must be another constant factor.

I wish to review some experimental work on hydronephrosis, done in collaboration with Dr. Frank Hinman and published in 1925, which demonstrated a fundamental principle in the mechanism of renal dilatation following urinary obstruction. I feel that this principle can be applied to an explanation of the origin of large cysts of the kidney. For the sake of clearness it will be necessary to give here some of the details of this work (191, 192, 193, and 194).

THE CIRCULATORY FACTOR IN RENAL DILATATIONS

In a study of the development of hydronephrosis it was found that if a ureter is completely obstructed the degree of hydronephrosis which develops is in direct proportion to the duration of the obstruction (Fig. 20). With a standard uniform rate of development as a control, it was possible to test the effect of various modifications of the renal secretion, such as diuresis, oliguria, splanchnotomy, compression of the renal vein, ligation of the venus collaterals, etc. on this rate. The most interesting and unexpected results were obtained in those experiments in which we directly modified the renal circulation by interference with the renal artery.

Group I.—*Arterial compression plus ureteral obstruction* (*192*). For example, in one group of dogs after ligation of the ureter, a

Fig. 19. Large, serous cyst associated with several smaller ones in an arteriosclerotic kidney. In size, gross appearance, and histologically it resembles in every detail the cyst in Figure 17 and differs from it only in that the etiology here is evident, in Case 6 it is not. (Case 7.)

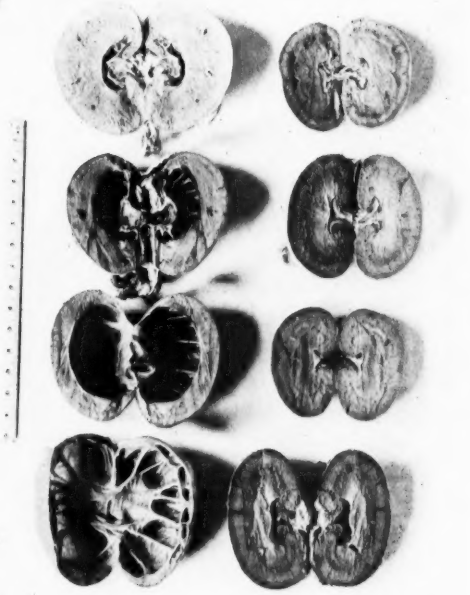

Fig. 20. Progressive development of hydronephrosis in direct proportion to the duration of the obstruction after complete ureteral block. The specimens at left represent a 7 day, a 14 day, a 28 day, and a 56 day hydronephrosis in dogs after ligating the right ureter. At right, normal kidneys.

permanent, uniform, partial constriction of the renal artery was produced by a small piece of rubber tubing, which was split and fastened about the artery (Fig. 21). This reduced the blood supply to the kidney to a degree, which, although it permitted urinary secretion to continue evidently at a greatly diminished rate, produced rather a marked anæmia.

When these dogs were sacrificed at varying periods and the hydronephrosis that followed ligation of the ureter was compared with control hydronephroses for the same period, it was found that there was a constant, progressive increase in the rate of development; that is, despite anæmia and evident reduction of urinary secretion, when the artery was compressed, the dilatation was much greater than when the blood supply was not disturbed. Figures 22 to 25 illustrate this variation.

It will be noticed that this increased rate of development was not occasional but was constant and progressive throughout the series. This variation was accounted for by assuming that the anæmia produced by the arterial compression resulted in a parenchymal degeneration, which weakened resistance in the kidneys and permitted a more rapid process of distention. In other words, the anæmia reduced tissue tone and favored relaxation to back pressure from ureteral obstruction.

Group II—*Arterial ligation plus ureteral obstruction* (*194*). The importance of blood supply to dilatation after ureteral obstruction was further demonstrated in another group of animals in which, in addition to tying off the ureter, one branch of the renal artery was ligated. The renal artery is divided into anterior and posterior branches. They are end arteries in the true sense of the word, so that ligation of either branch will result in infarction in the area which that branch supplies. Figures 26 and 27 demonstrate the area of distribution of the anterior and posterior branches

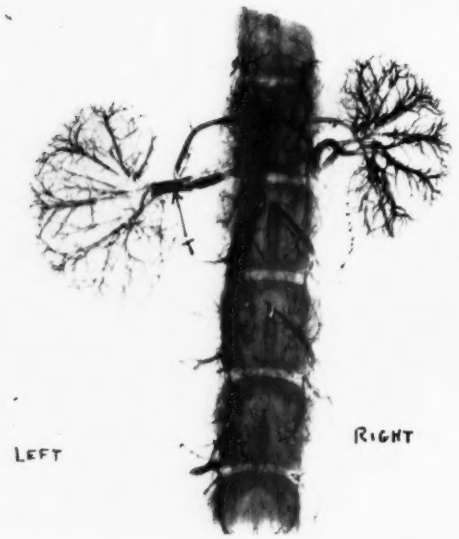

Fig. 21. Roentgenographic appearance of arterial barium sulphate injection of 7 day hydronephrosis of the left kidney of a dog with partial compression of the left renal artery; thinning out of the arterial tree of the left kidney as compared with the right, due in part to the compressing tube, *T*, which can be seen in place at the hilum.

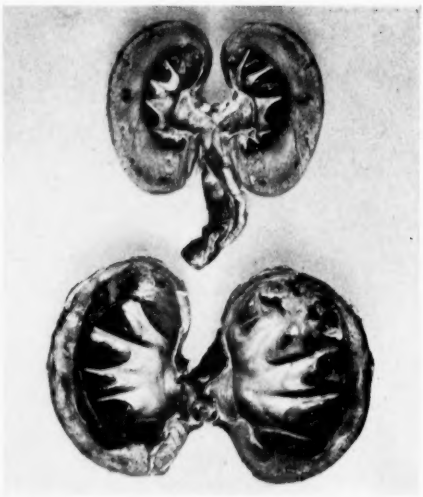

Fig. 22. Lower, 14 day period hydronephrosis in a dog with partial compression of the renal artery; upper kidney is used for comparison, and represents the degree of hydronephrosis seen with simple ureteral obstruction for the same period; remarkable acceleration in the rate of hydronephrotic atrophy when the artery is compressed.

in a rabbit's kidney. The pathological changes are those of anæmic infarction, with cloudy swelling, hyaline degeneration followed by fibrosis and atrophy (Fig. 28).

When the ureter was ligated and the posterior branch of the renal artery tied off, the unique condition shown in Figure 29 was found after 14 days. The posterior one-half of the kidney, which had been infarcted, ballooned out into an enormous diverticulum which communicated by a small opening with the hydronephrotic pelvis in the anterior one-half of the kidney the blood supply of which had not been disturbed.

Figure 30 shows a section of the sac or diverticulum and the fenestrum which opened into the pelvis of the anterior one-half of the kidney. The same result was obtained in nearly all the rabbits on whom the combined operation was done. Figures 29 to 35 show the specimens for varying periods of obstruction.

That the location of these diverticula is dependent on the area of infarction is beautifully illustrated in the specimen shown in Figure 35. In this experiment, in addition to the ureteral block, only a small arterial branch to the lower pole was sectioned, and the urinary back pressure besides producing a hydronephrosis in the normally vascularized portion of the kidney caused a blow-out which was limited exactly to the area which had been deprived of its blood supply. The sac wall in all instances was made up of fibrous connective tissue which was formed by the compression of the infarcted parenchyma by the urinary back pressure (Fig. 36).

What has happened in this group is that the urinary back pressure produced by ureteral ligation is exerted equally in all directions in the kidney and meets little resistance from the degenerated area, which has been deprived of its blood supply. As a result this balloons out into these enormous sacs, which can be compared with blow-outs.

In the first group, where the artery was compressed, the anæmia was uniform and the increased rate of dilatation general. In the second group, where the one branch of the artery was ligated, the anæmia was localized and complete (infarct), and the dilatation was correspondingly localized and extremely rapid.

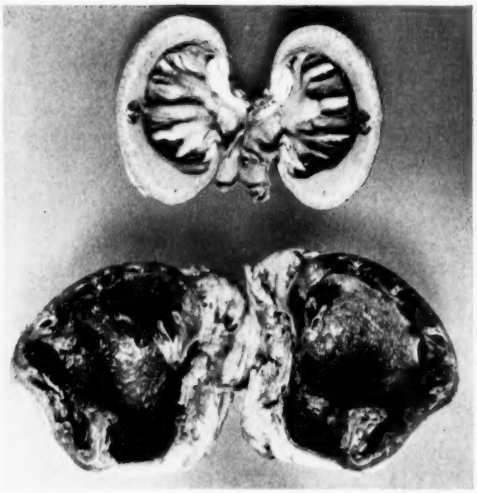

Fig. 23. Lower, 21 day hydronephrosis in dog following complete ureteral block and partial compression of the renal artery; upper kidney is used for comparison and represents the degree of hydronephrosis following simple ureteral block alone for the same period.

Fig. 24. Lower, 28 day period hydronephrosis in a dog with partial compression of the renal artery; upper, simple hydronephrosis for the same period.

These experiments established the importance of blood supply and local nutritional disturbances in the mechanism of renal dilatations from urinary obstruction and also in the process of repair, which follows relief of obstruction. I feel that the principle involved can be applied to our understanding of the mechanism of the production of these large solitary cysts.

APPLICATION OF THIS PRINCIPLE TO THE PATHOGENESIS OF SOLITARY CYSTS

I was struck by the similarity not only of the gross appearance but of the histological structure of these experimental diverticula to the first case of solitary cyst which I have reported. This gave rise to the idea that the important factor, disturbance of blood supply, in the mechanism of the production of the former might be concerned in the origin of the cysts.

Although group tubular block alone cannot produce them, it is conceivable in the light of the experimental work that, if the same condition which produced the tubular obstruction interfered with the arterial supply to the same segment of the kidney introducing the factor of parenchymal anæmia and degeneration, which favors tissue relaxation and rapid dilatation, then a cyst might form.

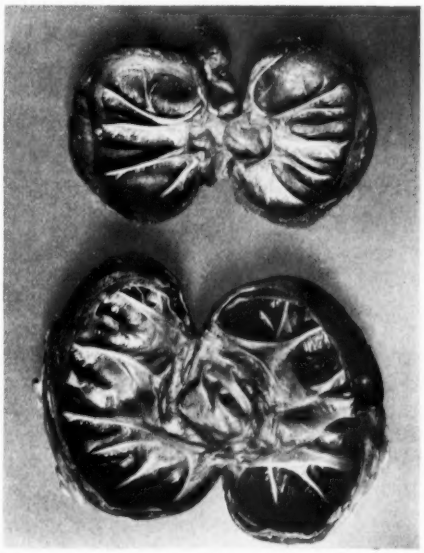

Fig. 25. Lower, 56 day period hydronephrosis with partial compression of the renal artery; upper, simple hydronephrosis for the same period used for a control.

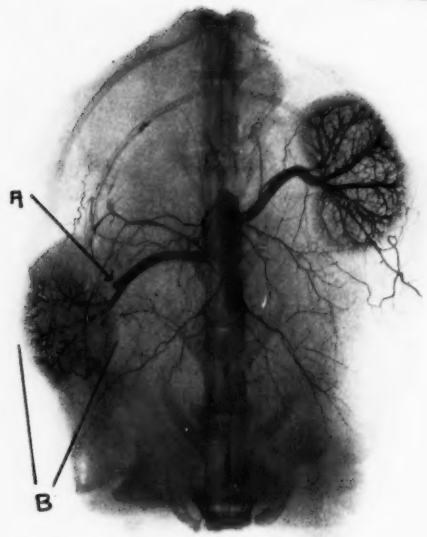

Fig. 26. Roentgenogram of a barium sulphate injection of the renal arteries in a rabbit. The anterior branch of the left artery has been divided between ligatures at *A*. The injection demonstrates the usual area of distribution, *B*, of the posterior branch.

In the experimental condition the urinary back pressure is produced artificially by ligating the ureter and the parenchymal anæmia

Fig. 28. Margin of infarct 7 days after ligation of posterior branch of renal artery; lighter area to the right represents the infarct; degenerative changes are marked.

Fig. 27. Sagittal section of injected kidney shown in Figure 26 demonstrating the relative distribution of the anterior and posterior branches of the renal artery. The posterior branch is injected.

by ligating a branch of the renal artery. In the cysts the intrarenal urinary back pressure is produced by group tubular obstruction and the parenchymal anæmia by the implication of an arterial branch in the region of the block in the process (Fig. 37). With active glomerular function continuing distal to the lesion rapid dilatation takes place. The surrounding kidney undergoes a compression atrophy and produces the connective tissue wall of the cyst. In some instances the fibrous tissue substitution is complete, in others there are still remnants of parenchyma in the sac wall. The obstructive factor, whether it be obliterating endarteritis with peritubular sclerosis, atherosclerosis, infarct, tumor, or what not, is involved in the process, hence all gross evidence that it was concerned in the formation of the cyst is eventually lost.

It is, of course, understood that the conditions mentioned are fairly common with well recognized pathological sequences. These lesions will produce a cyst only when they are so located as to cause group tubular obstruction with active glomerular function distal to the lesion and when, because of them, there is nutritional disturbance in the same segment of the kidney.

EXPERIMENTAL PRODUCTION OF SOLITARY CYST

An hypothesis of this kind, no matter how much the clinical features or pathological findings may support it, would carry little

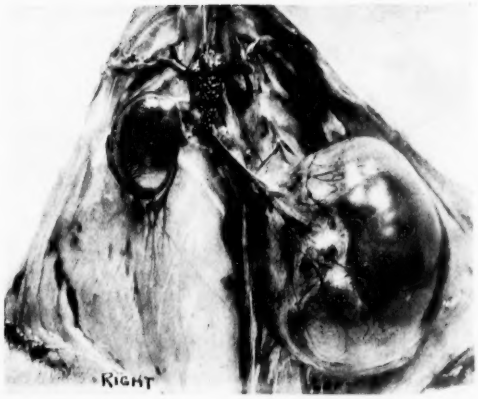

Fig. 29. Gross specimen *in situ* 14 days after ligation of left ureter combined with ligation of posterior branch of renal artery; anterior half of kidney embedded in the large saccular dilatation of posterior half, which has been deprived of its blood supply.

Fig. 30. Section of the diverticulum which was produced by simultaneous ligation of ureter and the posterior branch of the renal artery. *A*, Opening into the hydronephrotic pelvis of the anterior one-half of kidney the blood supply of which was not disturbed; upper, simple hydronephrosis for the same period.

weight unless it could be backed by experimental proof. Two investigators, Peterson (198) and Tollens (201), have attempted to produce cysts by obstructing the tubules, one with a silk suture about a papilla and the other by cauterizing the tip of a papilla. They obtained definite dilatation of the tubules but nothing which resembled a cyst.

If our conclusions are correct and if a localized arterial disturbance or parenchymal anæmia is a factor in the formation of these cysts, then its introduction is a simple matter by ligating one small branch of the renal artery in addition to blocking the tubules.

The rabbit's kidney is especially well suited for this type of experiment because it is a one-lobed kidney and therefore has but one papilla (Fig. 38). It would be difficult in a multilobed kidney similar to the human to pick out one papilla for obstruction and then be sure in ligating one branch of the artery that the infarct would be in the same segment of the kidney. In the rabbit all the collecting tubules can be blocked at one time and when a branch of the artery is ligated, urinary back pressure is sure to be exerted on the infarcted area. The following experiment was done.

Protocol—July, 1928. The kidney in a rabbit, weighing 3 kilograms, was exposed through a lumbar incision. The papilla was everted through a small incision in the renal pelvis and was fulgurated thoroughly to block the tubules. This incision was

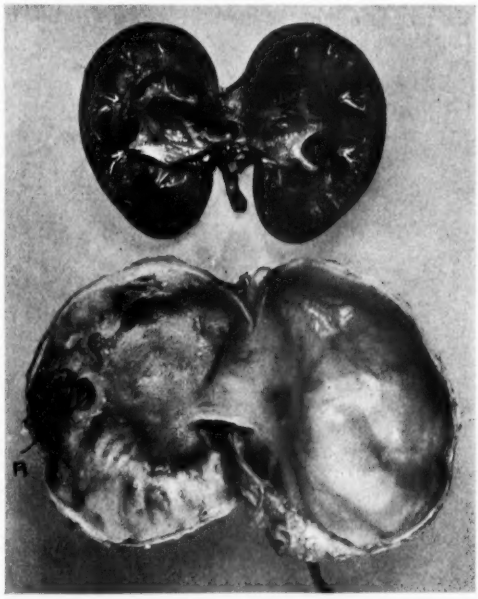

Fig. 31. Same condition as illustrated in Figure 30 for a 21 day period of obstruction. Saccular dilatation of infarcted posterior one-half of kidney. *A*, Opening which communicated with the hydronephrotic pelvis of the anterior one-half; upper, control 21 day hydronephrosis.

Fig. 32. Section of anterior one-half of kidney the blood supply of which has not been disturbed, showing hydronephrotic pelvis which communicates with saccular dilatation of the infarcted posterior one-half of kidney seen behind. Twenty-one day period of obstruction.

closed with a fine silk suture. The posterior branch of the renal artery was ligated, and the lumbar wound was closed. The rabbit was sacrificed after 18 days. Figures 39 to 41 show the condition found.

A cyst was produced similar in every way to the ordinary solitary cyst of the kidney. It did not communicate with the renal pelvis. The ureter passed behind it. It arose from the infarcted area. Figure 40 shows another view of the cyst with the ureter running behind it and the infarcted area.

A sagittal section of the kidney (Fig. 41) showed the normal pelvis, the place where the papilla was fulgurated, and the thick-walled cyst. The wall was made up of fibrous connective tissue (Fig. 42).

The confirmation of this theory of the mechanism of cyst formation is contained in the photomicro-

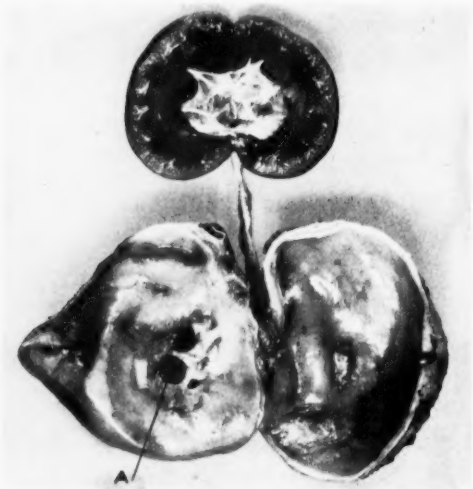

Fig. 33. Same condition as illustrated in Figures 29 to 32 for a 28 day period of obstruction. *A*, Opening into the hydronephrotic anterior portion.

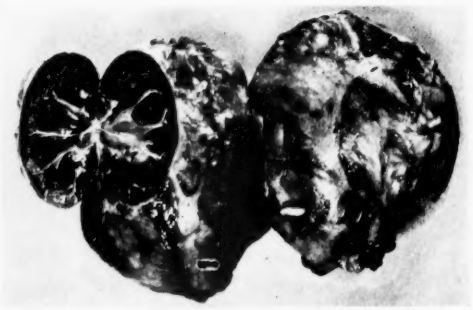

Fig. 34. Anterior one-half of kidney of the 28 day specimen. Note the hydronephrosis of the anterior one-half which communicates with the diverticulum behind.

graphs shown in Figure 43. It shows the normal parenchyma with dilated tubules, for it must be remembered that all of them were obstructed in the papilla. There is also the area deprived of its blood supply with hyaline changes and degeneration and then the cyst wall arising from this area with a complete connective tissue substitution.

Let us briefly consider how the lesions obliterating endarteritis with peritubular sclerosis,

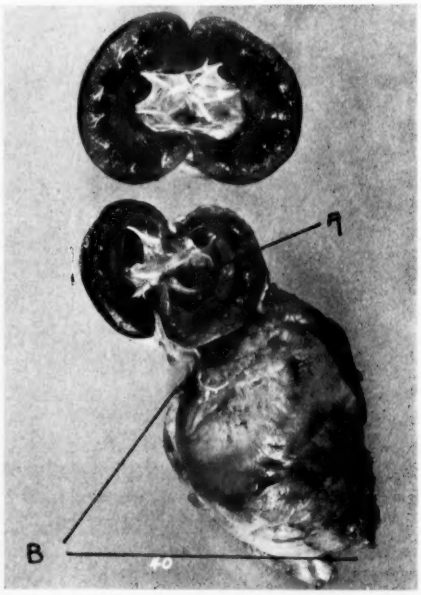

Fig. 35. Twenty-eight day hydronephrosis with ligation of arterior branch of lower pole; effect of the increasing pelvic pressure on the infarcted area, in this case limited to the lower one-third of posterior one-half of kidney. *A*, Communication between dilated pelvis and diverticulum, *B*.

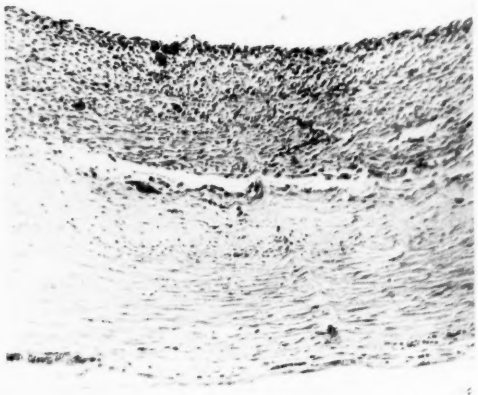

Fig. 36. Photomicrograph of wall of a diverticulum produced by infarcting portion of kidney and then blocking the ureter. There is a complete connective tissue substitution. Compare with wall of solitary cysts, Figures 7 and 42.

atherosclerosis, infarct, tumor, etc., which we assume could be etiological factors, might cause the combination of circumstances essential to cyst formation.

There is no question but that the mechanism described is operative on a small scale in the formation of the multiple small cysts in the arteriosclerotic kidney. The following is paraphrased from Mallory (197). "There is an obliterating endarteritis with sclerosis of the groups of arterioles and glomeruli and as a result nutritional disturbances of the adjoining parenchyma. The subtending tubules atrophy, and there is a connective tissue substitution. Small groups of tubules, the glomeruli of which are not involved become occluded by the peritubular sclerosis and there is dilatation with cysts." They are multiple because the process in the arteriosclerotic kidney is diffuse and small because the smaller vessels are involved. Hence the nutritional disturbance is confined to small area and the tubular obstruction to small groups.

It is conceivable that with occlusion of larger vessels, large cysts might form on the same basis. This would be especially likely in the focal form of atherosclerotic nephropathy (atherosclerotic kidney of Ziegler) in which the process is not diffuse, involves only certain of the renal vessels, often those of large caliber.

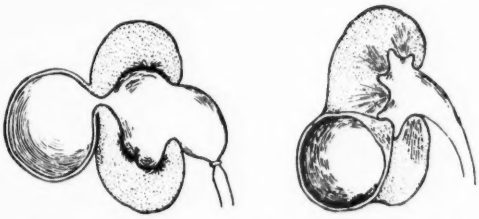

Fig. 37. Diagrammatic comparison of mechanism of production of experimental diverticula and of solitary cysts. *A*, Experimental diverticula: Urinary back pressure produced by ligating ureter and parenchymal anæmia by sectioning one branch of renal artery. *B*, Solitary cysts: Urinary back pressure (intrarenal) produced by group tubular block and parenchymal anæmia by implication of an arterial branch in the same process which produced the tubular block.

The relationship of at least some of these large, serous cysts to nephritis cannot be denied. In 28 of the reported cases, there were definite nephritic changes, chiefly vascular. In 25, the larger cysts, reported as solitary, were associated with smaller ones, similar in every detail except size and indistinguishable from those seen in nephritis.

It is not contended that all large serous cysts arise on this basis, but it does not seem that size should preclude the possibility of some of them at least having this origin.

It is also conceivable that a single infarction from embolus or thrombosis might produce a cyst. In the majority of instances such a lesion results in a wedge-shaped infarct with subsequent scarring and contraction. However, if one of the smaller vessels of the corticomedullary zone were involved and the lesion so situated as to have distal to it active, functioning glomeruli, then a cyst might form. The area of infarction undergoes a compression

Fig. 38. Illustrates an unilobed kidney. Section shows single papilla at *P*.

Fig. 39. Solitary cyst produced experimentally in rabbit's kidney.

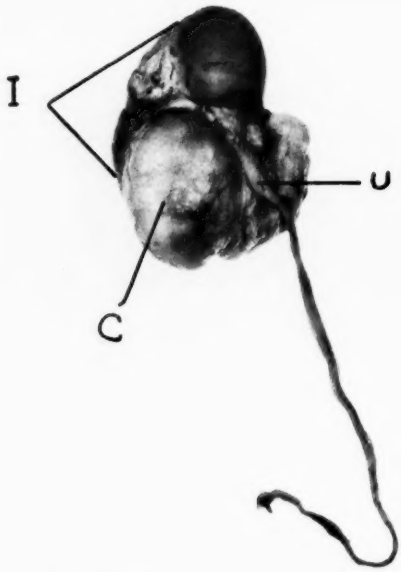

Fig. 40. Photograph illustrating, *I*, infarcted area from which arises, *C*, cyst; *U*, ureter passing over cyst.

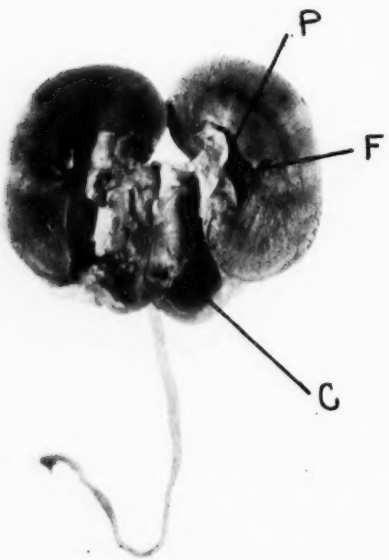

Fig. 41. Section of kidney showing, *P*, normal pelvis; *F*, area of papilla which was fulgurated; *C*, thick-walled cyst which does not communicate with pelvis. Portion of left half removed for microscopic section.

atrophy and becomes together with the compressed surrounding parenchyma the connective tissue wall of the cyst. Hence all evidence that it was concerned in its formation is eventually lost.

The same holds true for tumors. Neoplasms arising in the medulla might produce the combination of tubular block and arterial occlusion. When this occurs, the area blows out into a large cyst, usually hæmorrhagic because of the tendency for tumors to bleed. What would have been a hypernephroma or an angioma becomes a large, solitary hæmorrhagic cyst with barely discoverable remnants of tumor tissue in the walls. These are the only evidence of its origin because the original tumor became involved in the compression atrophy and together with the compressed surrounding parenchyma forms the wall of the cyst. The character of hæmorrhagic cysts would suggest that in many, in addition to the tubular block, the intrarenal pressure is furnished by repeated hæmorrhages into the parenchyma. A primary, simple hæmorrhage might become absorbed, or if fairly large,

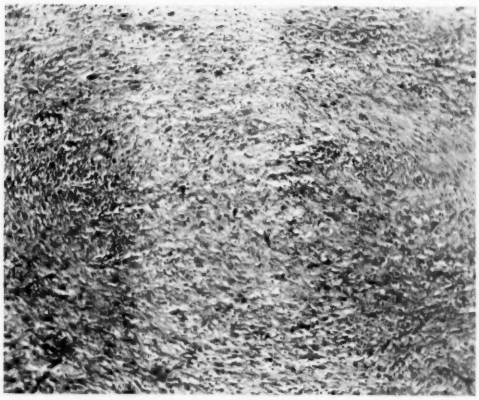

Fig. 42. Photomicrograph of cyst wall showing the same connective tissue replacement as occurred in the pelvic diverticulum produced experimentally and in the solitary cysts. Figures 7 and 36.

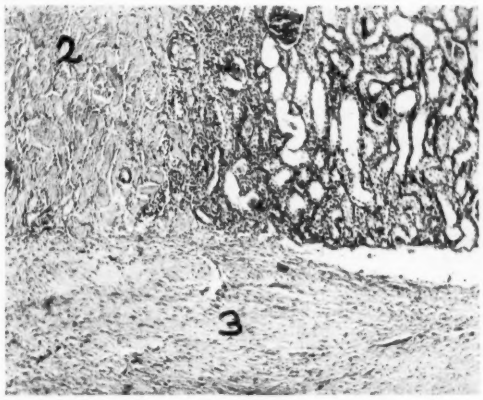

Fig. 43. Section at the point of contact of the experimental cyst with the kidney, showing: *1*, normal parenchyma, the blood supply of which was not disturbed but with dilated tubules from the obstruction produced by fulguration of papilla; *2*, area deprived of its blood supply by ligation of one branch of renal artery; *3*, wall of cyst which arises from this area.

encapsulated, and a small cyst form, but with such lesions as aneurisms, angioma, and hypernephroma, frequently associated with these cysts, the bleeding would tend to be repeated and furnish the intrarenal pressure.

SUMMARY

This conception can be briefly summarized as follows: These large, usually solitary cysts of the kidney are acquired. They are not a distinct entity with a common etiology but the mechanism of their production is essentially the same. Recognized pathological conditions of the kidney cause them but only when so situated as to produce a combination of group tubular obstruction and anæmic degeneration of the parenchyma from circulatory disturbances, in the same segment of the kidney. In some instances an additional factor is repeated prolonged hæmorrhages into the same area.

This conception explains the variation in size, number, contents, cyst wall, and associated renal conditions on the basis of variation of the direct etiological factor, the amount of group tubular obstruction and the area of nutritional disturbance depending on the size and distribution of the vessels involved. It also explains the apparent absence of a direct etiological factor in some instances, for the original lesion may become so involved in the process that all evidence of its presence is eventually lost.

Among the clinical and pathological features of large, renal cysts, which lend support to this hypothesis are:

1. The average age incidence of 45 years, a period when vascular lesions as arteriosclerosis, endarteritis, aneurisms, infarcts, and acquired lesions, such as tumor, are common.

2. The rather frequent association of these cysts with lesions, which might produce the conditions assumed to be necessary for their formation.

3. The frequent presence in the kidney containing a so-called solitary cyst of smaller cysts similar to the larger in every detail except size and indistinguishable from nephritic cysts.

4. The presence in the sac wall of groups of atrophied glomeruli and tubules, indicating its origin from renal parenchyma, which has undergone a compression atrophy with a connective tissue substitution.

5. The presence of remnants of neoplasm in the walls of many of the hæmorrhagic cysts as the only indication that tumor was concerned in their formation.

6. In many instances the sudden onset of symptoms, comparatively short clinical course,

and rapid growth of the cysts which can be easily understood in the light of the experimental work in which the enormous diverticula formed in a few days.

Finally by creating experimentally the conditions assumed to be necessary for cyst formation, we have been able to reproduce a large solitary cyst similar in every detail to those found in the human kidney.

Since the completion of this paper, solitary cysts of the kidney have been reported by Cibert, Hueper, Lewis and Carroll, Lucri, Rebizzi, Salleras, and Secretari.

I wish to express my thanks to Drs. Dudley, Mosiman, Lippincott, and McKinney for permission to study their specimens and to report their cases (Cases 2, 3, 4, 5).

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194. Idem. Arch. Surg., 1926, xii, 830.
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AN INQUIRY INTO THE BASIC CAUSE AND NATURE OF CERVICAL CANCER[1]

II. The Relation Between Cervicitis (Erosion of the Cervix) and Cervical Cancer

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THE RELATIVE AGE, FUNCTION, AND STABILITY OF SQUAMOUS AND COLUMNAR CELLS—METAPLASIA

THERE is no doubt that epithelial cells concerned in the covering of tissue surfaces, being produced at varying stages in the formation of the structure to which they belong, may be said to possess a certain age relation to one another—a distinction by no means as definite as that existing between true embryonic cells and adult tissue cells, but analogous to that represented by the distinction between, say spindle cells and adult muscle fibers, often observed in association. For instance, it is obvious, in dealing with squamous epithelium, that the upper and outer layers of cells are older than the lower and deeper ones. In the cervix uteri the outer layers of squamous cells are progressively flattened until those at the surface have become compressed into a thick protective covering of toughened tissue composed of the membranes of the cell walls concerned and containing scattered compressed nuclei. The surface of the cervix, however, usually remains smooth and fleshy, and in this way is distinctive from a tissue such as the skin, which is similarly covered histologically, but which possesses a hardness to its surface due to the keratin in the stratum corneum which is present in very minor degrees in the superficial cells of the cervix. Immediately below this outer covering there is a layer varying in depth consisting of semi-flattened cells possessing thick walls, no protoplasm, and ill defined nuclei. This layer merges insensibly into the polyhedral type of cell which makes up the bulk of the epithelial structure. The protoplasm and nuclei of these cells stain well. The lowermost layer, one cell in thickness, immediately abutting on to the subjacent tissues, is columnar in type, though often cuboidal in shape. The most active cells of this epithelial structure are those of this deepest layer. It is from these columnar cells that new polyhedral cells are produced in the event of proliferative activity. The nuclei of the lowermost polyhedral cells stain more deeply and sharply than the more superficial ones. The same may be said of their protoplasm. These facts are indicative of youth on the part of these cells. The nearer the polyhedral cells are to the basal columnar layer, which is a primary layer, the newer or younger they are. As one proceeds toward the surface one observes the fading of the protoplasmic contents of the cells, together with the diminution in density and distinctness of this nuclei. This aspect is tantamount to the passage from activity to passivity and proves the fact that the polyhedral cells possess only the mechanical protective function. Eventually these cells merge into the flattened type above mentioned. Cell production is carried on at the base of the epithelium, the former basal cells being forced upward toward the surface.

A normal epithelial covering, one which has not been called upon to exert cell activity, should therefore consist of a narrow band of cells, a relatively wide portion of which should be composed of extremely flattened surface cells—significant of long standing quiet on the part of the deepest layer—and no intermediate newly formed cells of the type just described.

Figure 14 shows a normal unaffected squamous covering to the cervix. The superficial compressed or semi-horny layer occupies approximately half of the total depth of the epithelium and abuts directly on to the cells of the malpighian layer, the lowermost layer of which is composed of cells of a low columnar type. This is often the case though by no means always is the lowermost layer definitely of a columnar type. One might, however,

[1] Part 1, "The Pathology of Cervicitis," appears in March, 1930, l, 513-532.

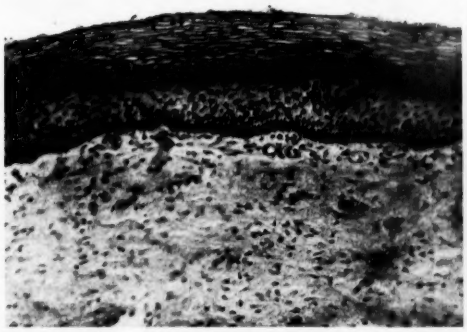

Fig. 14. A normal squamous epithelial covering (cervix). Total depth small. Relatively wide depth of compressed surface cells. Lack of intermediate semiactive cells. Lowermost layer low columnar in type. Complete lack of inflammatory reaction. A thin layer of cells corresponding to stratum granulosum beneath superficial cells.

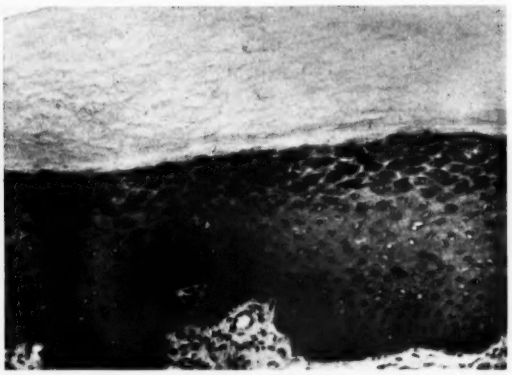

Fig. 15. Squamous epithelium, showing, first, an excessively thickened and keratinized superficial layer, and second, a definite stratum granulosum. Photomicrograph of section which was taken from a hypertrophied cervix which possessed an excessively thickened skin-like covering.

say that it is made up of cells which are distinct morphologically from those of the malpighian layer, and are of the columnar type, though often cuboidal in shape, a fact which I attribute to an excessive degree of pressure.

The cervical squamous epithelium occasionally shows a well marked stratum granulosum running between the flattened superficial cells and the malpighian layer. This is, however, but poorly marked in the majority of cases, as compared with that observed in the squamous epithelium of normal skin, and if, as according to Ranvier, the granules of eleidin which these cells contain are used for transference into the keratin of the more superficial strata, it would appear that their function is not so necessary in the case of the cervix, which has a relatively soft surface, as it is in the case of skin. In Figure 14 one may observe a thin line of cells in this position which stain rather more deeply than do the cells of the malpighian layer immediately below them.

Figure 15 is taken from a hypertrophied cervix possessing an excessively thickened surface, the superficial flattened cells of which have more right to the term *stratum corneum* than have those of the vast majority of cervices. Here one may observe a very definite stratum granulosum, activity on the part of which has evidently been called for in the supply of keratin for the excessively thickened and horny superficial layers. I consider, however, that activity on the part of the cells of the stratum granulosum is largely functional in this way, and I do not believe that they are concerned in any way with the cancerous reactions of this epithelium as a whole.

The basal columnar cells of the malpighian layer however react by proliferation to irritative stimuli. An inflammatory reaction in association with these cells produces multiplication of them by cell division. A percentage of the cells thus produced become displaced from immediate contact with the irritant and revert to passivity. New basal cells continue to proliferate. The thickness of the epithelial covering is increased and the new cells out of contact with the irritant take up an intermediate position between the stratum granulosum and the lowermost layers. These newly formed cells possess nuclei and cytoplasm which stain deeply. They are polyhedral in shape and have relatively thin walls. These new cells, now intermediate in position, are seen to be undergoing gradual flattening as they near the surface, i.e., as they become relatively old. Their walls become gradually thicker and their nuclei and cytoplasm gradually diminish in amount

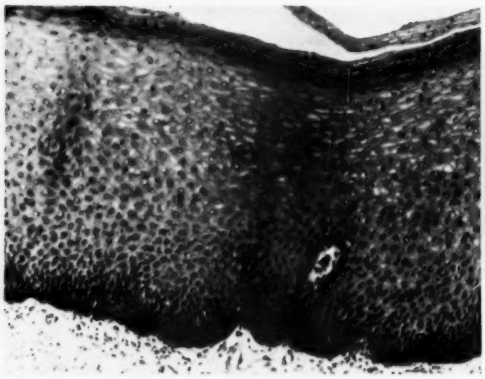

Fig. 16. The effect of a low grade irritant on the epithelial covering. The epithelium is much thickened. The superficial compressed layer is relatively thin. The new intermediate cells of the malpighian layer are very well marked.

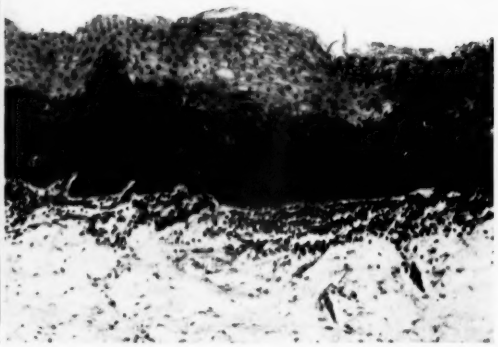

Fig. 17. A low grade infection irritating the basal layer of a normal squamous epithelium. Proliferative cell division among columnar cells, leading to formation of new cells of rete mucosum. A loose leucocytic infiltration beneath epithelium. A localized "doubling" of basal layer.

and concentration the farther they are situated from the basal cells from which they have sprung. Obviously a gradual retrogression due to advancing age in association with entire lack of function.

A squamous epithelial covering, therefore, which exhibits these intermediate cells in fair degree, thereby lessening the relative thickness of the superficial compressed layer, shows histological proof of its having been subjected, at one time or another, to an irritative reaction affecting its basal layers. The greater the thickness occupied by these intermediate cells, the more the proliferation that has occurred from the basal layer and consequently the longer has the irritation been continued. Examples of this type of mild reaction are to be found in long standing hypertrophies of the cervix, in the causation of which a low grade infection has played a part.

Figure 16 is taken from a case of this type. The squamous epithelium here shows its reaction to a low grade infection which has become subdued and the evidences of which are now extinct. One observes the increased thickness of the covering epithelium. This is almost entirely due to the intermediately placed, relatively young cells which can be seen to change gradually as they near the surface from possessing the histological features of the new cell to that of the older surface cell. It will be noticed that during the course of this change, the cells lose their cytoplasm much more readily than their nucleus, which still remains even in certain of the cells which have passed to the stage of almost total compression. The thickened epithelium is again lined basically with a low columnar type of cell, quite distinct from those in immediate contact with it, showing that this primary layer reasserts itself as such, after activity ceases.

In any given squamous epithelium, therefore, the youngest or most recently produced cells are those situated at the base of the malpighian layer or rete mucosum in contact with the basal columnar layer. The nearer the surface a squamous cell is, the older it is. A "young" or recently produced cell is relatively rich in the density of its cytoplasm. Its nucleus stains deeply and appears to be large on account of the relative smallness of the newly produced cell. Moreover, we shall see that the "younger" a cell is, the less stable it is. The older cells toward the surface of the epithelium, those that have lost their cytoplasm, and whose walls are becoming thickened, are incapable of reactive changes. Their nuclei, if still present, are inert. One may frequently observe instances in which these older cells are in contact with

Fig. 18. High power view of the primary cell division among the basal columnar cells. One may observe the process of nuclear division. The basal layer has begun to divide into two over a limited area.

Fig. 19. The low columnar cells of the basal layer of adjoining squamous epithelium encroaching by extension on to the old erosion area. Commencing regeneration of squamous epithelium originating from the basal layer.

surface infection, with failure to respond to the irritative stimulus. Desquamation results, due to maceration of sensitive cells beneath them. The younger cells, however, react in various ways according to the stimulus imposed. They are, therefore, unstable by comparison, and their instability to a given stimulus appears to be the greater the younger they are.

The all important layer, from the functional point of view, is the lowermost, that composed of the columnar type of cell. As I have previously said, the actual height of the cells composing this layer may vary enormously. It is to be readily understood that a columnar cell situated between an epithelium many layers in thickness and dense mesoblastic tissues is subjected to varying degrees of pressure along its length, and this fact no doubt plays an important part in the determination of the actual height of the cells concerned. In any case, however, there is no doubt but that the cells concerned in this basal layer, one cell in thickness, are of the columnar type, even though many instances may show them to be of a low columnar variety, or even cuboidal. A very large percentage of cases, however, show regular and very definite columnar cells in this situation, though of a small and closely packed type.

I say that this is the all important layer functionally because I believe that it is directly concerned in the production of the new (young) cells of the malpighian layer (rete mucosum). The study of my cases has shown me that it is by a primary cell division of these columnar cells that the proliferative changes are instituted in that region of the epithelium affected by the irritant stimulus. Active and repeated cell division on the part of these columnar cells leads to the production of cells of the polyhedral type which go to the formation of the new lower layers of the rete mucosum.

Figure 17 shows a case in which an otherwise perfectly normal squamous epithelium, one that has hitherto been unaffected by irritative stimuli and which exhibits histological characteristics similar to that described in Figure 14, is subjected to an inflammatory reaction of low degree, as evidenced by a relatively loose leucocytic infiltration immediately in contact with its basal layer. In the area shown one may observe the very beginnings of proliferative cell division taking place in the columnar cells of this layer. Under the low power the basal layer is seen to present a localized thickening and "double" appearance due to the primary division of the columnar cells. Under the high power magnification (Figure 18) one may definitely observe the process of nuclear

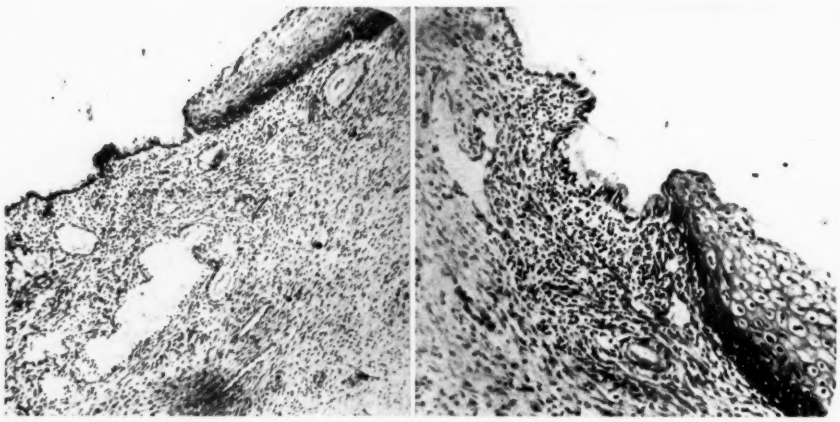

Fig. 20 (left). The normal junction between squamous and columnar epithelia at the region of the external os.

Fig. 21. The external os. A junction between the squamous and columnar epithelia. A subepithelial inflammatory reaction causes reactive thickening of the squamous but no change in the columnar epithelium.

division in many of the primary cells. The nuclei of these primary columnar cells are elongated in shape. After division, the nuclei of the resultant cells are still elongated, but it is possible to observe a rapid transition on the part of the newly produced cells to the polyhedral type after complete separation from the parent cells with a consequent rounding of the nucleus. This phenomenon takes place in the cells produced away from the base of the parent cell. The new basal cell retains its columnar shape, definitely if the irritation to which it is subjected is very slight and its reactive activity consequently slow, not so definitely if the irritation is intense, thus calling for rapid metaplasic activity. In this case the new basal cells tend temporarily to lose their definite columnar shape in the stress of severe involvement, but in all cases the true histological nature of this layer can be traced in lesser involved areas, and in all cases the type is definitely resumed on the cessation of activity. I will, therefore, assert that irritation below that of a destructive virulence affecting the columnar celled basal layer of the squamous epithelium, as evidenced by an inflammatory reaction in the vicinity, results in a true metaplasic activity on the part of these cells whereby they progressively produce new cells of the polyhedral type which are themselves physiologically inert but which, on account of their youth, are highly unstable in their powers of resistance to irritation. The proof of this assertion I hope to show as we proceed.

With regard to age of the cells entering into the composition of the squamous epithelial covering therefore, one may say that the basal columnar layer is the primary layer—that from which the epithelium is produced and hence its cells are the oldest. Moreover, they possess a physiological function, that of cell production by metaplasia. For the rest, the oldest squamous cells are those at the surface, the youngest at the base, and these are as yet polyhedral. Squamous and polyhedral cells have no physiological activity. Their function is purely mechanical —a protective one.

Like all cells, however, they exhibit the phenomenon of proliferation as a response to irritation and this phenomenon is more readily observed in the newly formed cells of the squamous epithelium than in the older ones, a fact which demonstrates the relative instability of the youthful cell.

In the commencement of healing of an erosion or even of ulceration of the cervix, when the elements of epithelium again begin to cover the erstwhile inflamed zone, it is

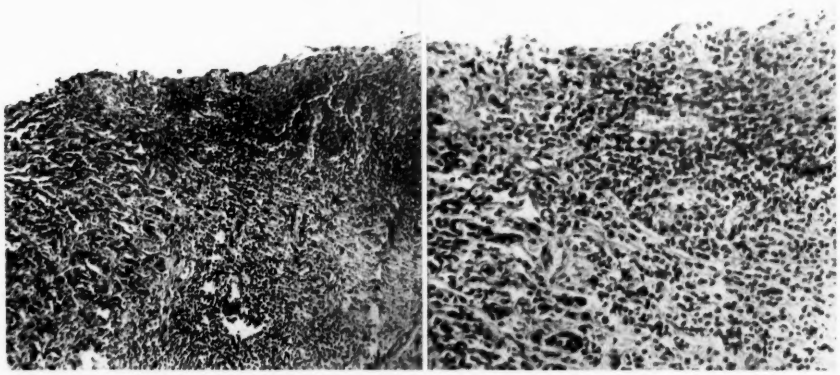

Fig. 22 (left). An irritant of first virulence attacking squamous epithelium. Relative depth of the infiltration is shown together with the slight reaction on the part of the adjacent epithelium.

Fig. 23. Contact site between squamous epithelium and irritant. Rupture of the basal columnar layers by the irritant. Local destruction of cells without reaction. Masses of macerated epithelial cells in the inflammatory exudate.

cells of the columnar type which first form the contact. These are primarily derived from the columnar epithelial cells of adjoining cervical glands by extension (see Fig. 4, low power, and Fig. 18) which are even more resistant to maceration than the columnar cells of the squamous basal layer, but are later replaced by these basal cells which extend from the base of the adjoining squamous epithelum and always precede the reformation of the new squamous covering. This fact is exemplified in Figure 19. Here one may observe this basal layer growing upward to the surface of the old erosion. It maintains its morphological character in so doing, although the height of the cells is not quite equal to that which normally appertains. There is a complete absence of surface inflammatory reaction in this case, so that the new columnar epithelium has been allowed to travel a relatively long distance without reacting to an irritative stimulus. A long strip of cells, therefore, has thus grown out from the adjoining squamous epithelium. The furthermost cells consist of only the one layer, basal cells themselves, but as one approaches nearer to the original epithelium this layer becomes two or three cells in thickness and there are isolated regions in which this thickness is locally increased to four or five cells. It is noticeable that the columnar type of the cell is definite where the layer is only one cell in thickness, but that the base of the thickened regions is composed of cells which are more cuboidal in shape. This I consider is undoubtedly due to the phenomenon of cell division having taken place in the basal layer with the consequent reproduction of polyhedral shaped cells which are extruded to the surface to become squamous

Fig. 24. The edge of an active ulcer. Old squamous epithelium. Subepithelial acute inflammatory infiltration of approximately one-third the density of the destructive force. Sharp epithelial downgrowths. Intact basal columnar layer showing metaplasic activity and protective function.

Fig. 25. Old squamous epithelium affected by an irritant of the first degree of virulence from below—being an increase from an irritant of the second degree. Dense acute inflammatory infiltration in contact with terminations of downgrowths.

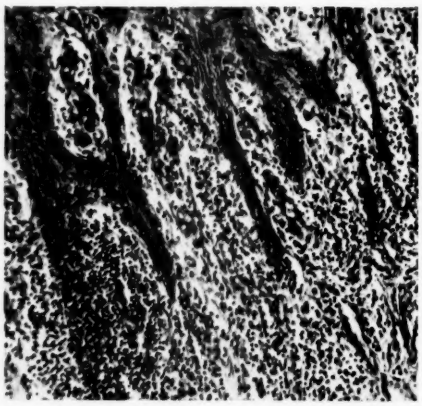

Fig. 26. Local destruction without cell reaction of terminal portion of cell downgrowth. Basal epithelial activity is present in the superficial rarefied zone. Columnar cell division is well shown.

in shape. This fact is in accordance with what we have seen when the basal cells react to irritation. When actively functioning they temporarily lose their definite columnar quality—a fact which is easily understood when one realizes that the cell function necessitates cell division. I, therefore, believe that during the process of repair in old erosions, the new squamous epithelium is produced by the active physiological activity of these primary basal cells, and not by direct growth extension from adjoining squamous cells. Indeed, as I have said before, I consider these cells to be physiologically inert, having owed their inception to the basal cells themselves, and being capable only of direct proliferation under stimulus as behooves cells the function of which is a purely mechanical one.

The question of the age, function, and stability of the elements of the squamous epithelium is now complete, but we must still consider in this section the same factors with regard to the columnar cells which line the cervical canal and glands. These cells differ morphologically from those just discussed, in that they are of the high columnar type, possessing well marked nuclei at the base and are ciliated. Normally their junction with the squamous epithelium in the region of the external os is abrupt, and serial sections of this region fail to show any definite continuity between them and the basal columnar cells of the squamous layer.

Figure 20 shows this normal junction. At its termination, the squamous epithelium tapers either abruptly or gradually, the basal columnar layer growing upward to meet a descending surface. The columnar cells of the canal join this termination abruptly, and there is no impression of continuance between them and adjoining cells.

We have already seen, in discussing the pathology of erosion, that the columnar epithelium is the most resistant to infection and irritation. This is exemplified by the fact that this epithelium is the first to proliferate to the surface of the affected area, which it covers while still proliferating in the primary effort to effect repair (see Fig. 4). These cells are thus in actual contact with an irritant, the virulence of which is sufficient utterly to destroy the original squamous epithelium *en masse*. We have seen moreover that it is not until this virulence is considerably diminished that the basal layer of the squamous epithelium again grows out on to the surface held by the columnar epithelium (see Fig. 6). The columnar epithelium, therefore, is much more resistant to maceration and hence more stable than any of the elements of the squamous epithelium.

Fig. 27. Long bulbous downgrowths resulting from continued irritation of the squamous epithelium from below by an irritant of the third degree of virulence.

Fig. 28. Large irregular bulbous downgrowths, some resulting from the filling of gland spaces. An appearance which might be mistaken for malignancy.

In examining large numbers of sections one is frequently struck by the fact that an inflammatory reaction of a density[1] which is always sufficient to call forth strong reactive changes in connection with squamous epithelium, effects no reaction when in contact with the normally situated, original columnar epithelium. Figure 21 again shows the junction between the squamous and columnar epithelia. There is a subepithelial inflammatory reaction present which has had the effect of thickening the squamous epithelium (by the process already discussed) but has had no effect upon the high columnar cells which maintain their evenness of continuity.

This distinction in reactive qualities between these two types of epithelium is not so obvious in a section such as this which shows the two in contact as it is in others where the effect of the same irritant can be observed but in different areas. We shall, however, meet with such instances later. My object, however, in this section is to show the great distinction in stability or resistance to irritation that exists between these two types of epithelium. It will be seen throughout that an irritant the action of which will produce destruction of the squamous epithelium will only produce a proliferative reaction in the columnar epithelium of the canal and glands; and that one which can produce proliferative changes in the squamous epithelium has no effect upon the columnar. The distinction goes much further than this, as we shall see, but thus far we are able to exemplify these two dissimilarities which will suffice in the attainment of the object in view.

In dealing with a structure one cell in thickness, the relationship in age of the cells does not enter, as it did when dealing with the squamous epithelium, but the function of these columnar cells is obviously that of a

[1] I shall later discuss the question suggested by this term.

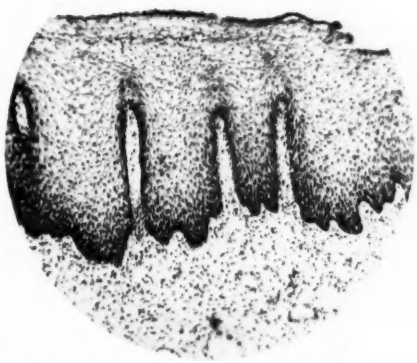

Fig. 29. The more regular and shorter downgrowths associated with transient erosion.

Fig. 30. Squamous downgrowth filling a gland space. New cell production laterally and old cells forced downward.

Fig. 31. A pseudo appearance of early malignancy produced by irregular bulbous downgrowths.

secreting epithelium, so that in all cases in which this epithelium is stimulated to the extent of proliferation, its resultant activity is always toward the formation of new glands. This we have seen to be the case when dealing with erosion.

We shall now proceed to consider the reactive changes produced in these various epithelial elements in response to the irritative stimulus, and to that end one must recognize the fact that cellular reactions will depend upon the strength or virulence of the particular stimulus to which they are subjected. A brief consideration of this factor must, therefore, take precedence.

Fig. 32. The effect of an irritant of the third degree upon long standing proliferated epithelium.

THE RELATIVE VIRULENCE OF IRRITATIVE STIMULI AFFECTING CERVICAL EPITHELIUM

During the histological examination of a large number of specimens, as in this series, one is constantly confronted with the fact that the irritative stimulus in contact with the epithelium, which is evidenced by the production of an inflammatory reaction in the vicinity, falls, for practical purposes, that is, according to the specific cellular reaction which results, into five main degrees. These may be called irritative stimuli of the first, second, third, fourth, and fifth degree of virulence in descending order. One may safely presume that the typical inflammatory reaction which is produced in living tissues in response to the presence in them of foreign bodies, atypical cell formations (tumors), chemical irritants, or infections by microorganisms, varies in density directly as the degree of irritation produced by these intruders. Without going so far as to make an actual comparison by cell count of the leucocytic and lymphocytic cells in affected areas under consideration, it has been quite obvious, during the routine study of the 850 cases of my series, that, from the point of

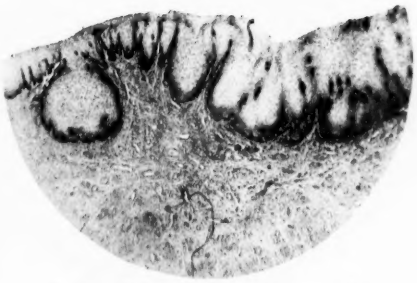

Fig. 33. General bulbous downgrowths.

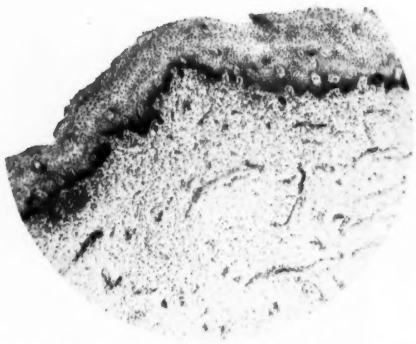

Fig. 34. Irregular small epithelial nodules produced as the result of a round cell infiltration of the fourth degree. A local infiltrative concentration can be seen. No subepithelial rarefaction. Narrow zone of newly produced cells.

view of cellular density in the inflammatory infiltration produced, the tissues under consideration have been subjected to irritations (no matter from what cause) which may be divided into five main degrees of virulence, and it is a fact that the resultant epithelial reactions correspond to a great degree of accuracy with the density of the infiltration which is in immediate contact.

One recognizes, of course, the fact that the reaction on the part of the tissues of the body, which is itself the instigator of these histological evidences, is governed by the resistance of these tissues to invading irritants —and hence is necessarily a varied factor even as the actual degree of irritation is varied. The action of an irritant of known virulence upon the tissues of one particular person will result in the production of an inflammatory reaction of a density differing from that produced by the same irritant in another host. These reactions would, of course, be regulated by the affected persons' powers of resistance, and histologically the cellular densities of the associated inflammatory reactions will differ in the two cases in either one of the innumerable (presumably) minor degrees, or even sufficiently to warrant placing this known irritant in separate main categories of virulence in each case, such as has been described. It will thus be seen that, owing to the presence of the varied factor of the patient's resistance, it is compatible with sound reasoning to suppose that a given irritant may produce tissue reactions in different hosts, the histological examination of which would place that irritant in different main categories of virulence. The five degrees of virulence, therefore, into which I have divided the irritants affecting cervical epithelium are purely relative—relative to the

Fig. 35. Uniform epithelial thickening in response to an irritant of the fifth degree of virulence. The columnar nature of the basal layer is well seen. A loose epithelial lymphocytic infiltration.

Fig. 36. High power view to show the definite columnar character of the basal layer and the process of cell production from this by metaplasia.

Fig. 37. General view of the effect of an irritant of the third degree of virulence upon new squamous epithelium (see "The Cancer Phase—Squamous Epithelium").

resistance of the host. Theoretically each degree might be produced by the same irritant. Again, any one degree might be produced by irritants varying in actual virulence. I have said above, however, that the effect of these five degrees of irritant upon the affected epithelial structures is constant to a high degree of accuracy as nearly as one can speak of constancy in connection with the human subject and without absolute mathematical accuracy of detail.

We have therefore two varying factors, (1) the actual virulence of the irritant and (2) the host's resistance, combining to the production of a definite histological phenomenon, which I will treat as a constant factor, on account of the constant effect produced by it—an inflammatory reaction of either of five cellular densities—to which a relative term in irritative virulence is applied indicative of the relationship of the varying factors mentioned; and these relative degrees of irritation have a constant effect upon cervical epithelium.

To complete this chain as it were, it would appear that one must expect the individual cells of cervical epithelium to react constantly to minute variations in the degree of irritative stimulus, and therefore to maintain themselves as constant factors in the schemes. Whether this be so, it is, of course, impossible to say, but in any case the absolute constancy of this terminal factor is not a necessity in so much as their type of reaction to irritation is histologically uniform, and, as the main degrees of irritative virulence are alone able to effect the important and constant distinctions in cellular change, one may safely presume that the included minor degrees are similarly uniformly reacted to.

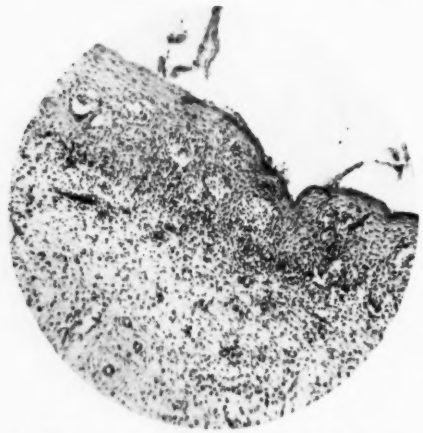

Fig. 38. The cancer phase—squamous epithelium. The earliest evidence of the inception of cancer change. Perforation of the basal layer by inflammatory exudate. A typical cell proliferation on the part of the new polyhedral cells. Typical blurring of general cell mass (see text). The spasmodic and localized metaplasic response on the part of the basal layer.

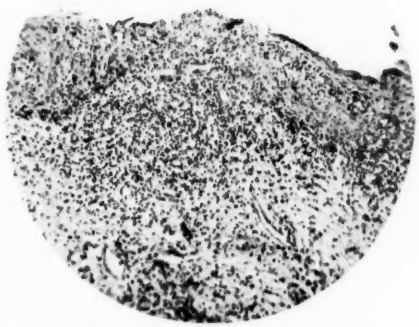

Fig. 39. Destruction of the new squamous epithelium without reaction, by contact with a localized increased density of the subepithelial infiltration corresponding to the first degree of virulence (see Figs. 22 and 23).

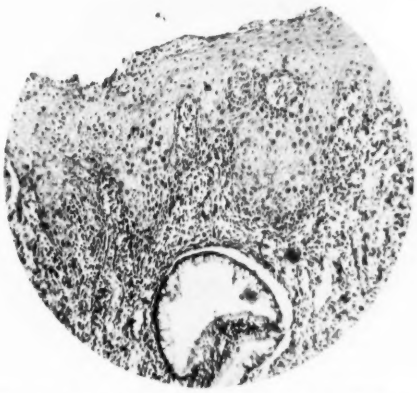

Fig. 40. The cancer phase—squamous epithelium. A somewhat farther advanced stage (see text).

While recognizing, therefore, that the degrees of density of inflammatory reaction in the human body are infinite, I have preferred here to divide them into five main degrees on account of the fact that cellular reactions, as I have observed them throughout the whole of my series, fall into five main types and these correspond accurately to the main degree of irritation in contact.

THE EFFECT OF THE ACTION OF AN IRRITANT OF THE FIRST DEGREE OF VIRULENCE UPON OLD SQUAMOUS EPITHELIUM

The picture here is one of complete and rapid destruction of the epithelial elements. The densest type of inflammatory reaction, consisting of masses of closely packed leucocytes and lymphocytes, envelopes the remains of the epithelial cells in the affected area. Destruction by maceration and liquefaction is carried out, without any effort to respond on the part of the epithelium. This type of reaction takes place in Stage 1 of so called cervical erosion. An acute irritant is in contact with an unprepared epithelium. Rapid destruction results. Among the masses of infiltrated leucocytes one may observe numerous areas of partially destroyed cells of the polyhedral type formally belonging to the deeper layers of the squamous epithelium. The infiltration penetrates relatively deeply from the affected surface, and quantities of dislodged squamous cells come to occupy positions at a much deeper level than they did originally since they are carried inward by the fluid exudate excited by the irritant. They are, however, at this stage partially destroyed and totally inert.

Figure 22 shows the type of density of the inflammatory reaction associated with an irritant of the first virulence and the depth to which the infiltration penetrates relative to the pre-existing epithelium.

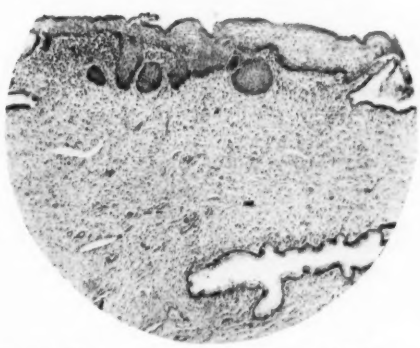

Fig. 41. The cancer phase—squamous epithelium. Another instance (see text).

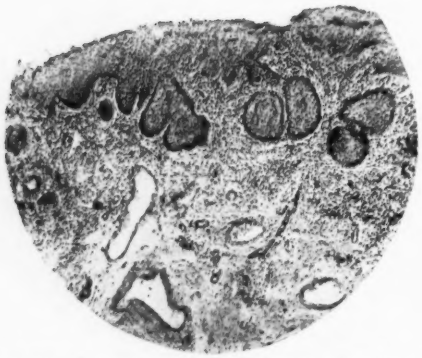

Fig. 42. The cancer phase—squamous epithelium. A more advanced phase bordering upon developed cancer.

Fig. 44. High power view.

One may observe in such a case that the epithelium adjacent to the affected zone shows only slight reaction. There is but a slight increase in its thickness showing that there has been no long continued action of the irritant upon it. What reaction there is, since such action is due to the increased production of new polyhedral cells by the stimulated basal layer, and these are plainly visible, corresponds accurately to that expected when this layer is in contact with the looser inflammatory infiltration, which is here observed as a prolongation from the main mass. There has been no time for epithelial reaction to take place to any extent along this lesser involved line. The transition between the denser infiltrative zone, in which the epithelial elements are destroyed, and the relatively unaffected areas is abrupt. That the squamous epithelium here has as yet been unaffected by previous irritants is shown by its total thinness, the relative scarcity of polyhedral cells, and thickness of its superficial flattened layers, combined with the lack of subepithelial rarefaction, a legacy of previous erosion. The density of the subepithelial tissues here is such that the cells of the basal layer of the epithelium are largely cuboidal in type. There is also no evidence here of old cervical glandular proliferation. We are dealing, therefore, with the effect of the most virulent irritant upon old, original, squamous epithelium, the composing cells of which should possess the highest degree of resistance to maceration possible to this type of cell.

Fig. 43. A very early developed squamous cancer (see text).

At the very point of contact, however, between the denser inflammatory infiltration and the adjacent epithelium, the basal columnar layer is broken through, and inflammatory cells infiltrate to some extent between the squamous cells. There is no reaction on the part of the superficial epithelial cells which are inert and purely protective. The lower polyhedral cells show abortive attempts at proliferation, but the irritant is too strong and its action too rapid at this site to allow

Fig. 45. The slight cellular reaction produced in glandular epithelium by contact with an irritant of the first degree of virulence.

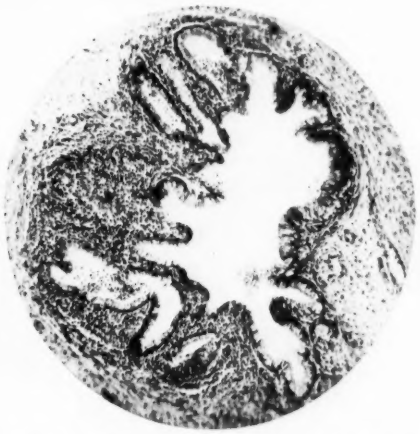

Fig. 46. The cancer phase—columnar epithelium. The cell reactions immediately preceding malignant change in young gland epithelium (see text).

resistance and local destruction is again observed here.

Figure 23 shows this area, which is, of course, common to all this type of case. Inflammatory infiltration into the substance of the squamous layers can be seen and the ruptured basal columnar layer is easily discernible. The lack of epithelial reaction to the irritant is definite. In this section one may also observe the isolated areas of half destroyed squamous cells at various levels in the densest part of the exudate. These cells are changed and varied in shape but tend to cling together for the most part in small groups.

Such is the effect, therefore, of an irritant of the first degree of virulence upon squamous epithelium. The picture is one of total and rapid destruction, and the cellular reactions conform in detail to this process. The reactions here described are observed in the first stage of so called cervical erosion. In this condition the full effect of the irritant is relatively transient. The resistance of the affected tissues is such that the process of cell destruction is soon stayed and the phenomenon of repair commenced. The adjacent epithelial structures, therefore, undergo little or no reactive change, but constitute the basis from which the ultimate repair cells emanate, as previously described.

THE EFFECT OF THE ACTION OF AN IRRITANT OF THE SECOND DEGREE OF VIRULENCE UPON OLD SQUAMOUS EPITHELIUM

The cellular reactions involved in this instance are observed in cases of true active ulceration of the cervix. The base of the ulcer consists of squamous epithelial elements destroyed by maceration in consequence of their contact with an irritant of the first degree of virulence. In the case of true ulceration, the resistance of the tissues is

Fig. 47. The cancer phase—columnar epithelium. A slightly more advanced stage. The earliest evidence of definite cancer change in new gland epithelium.

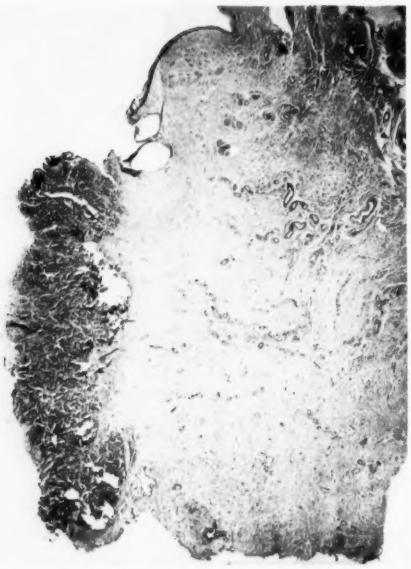

Fig. 48. Direct malignant proliferation from old gland elements in response to local and prolonged severe irritation.

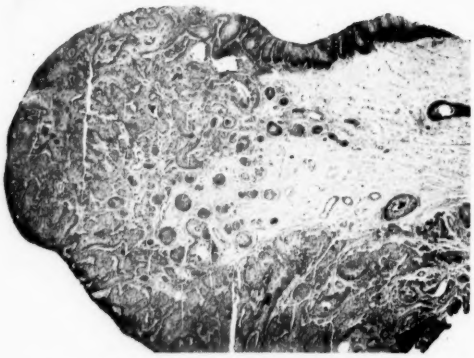

Fig. 49. A developed cancer. The contact between the benign and malignant tissues can be observed.

relatively poor. The process of invasion of the destructive irritant is inadequately stayed. The phenomenon of ultimate repair is delayed. The result is, therefore, that the zone of destruction is more permanent and pending the advent of the repair it becomes gradually transformed, by organization of the inflammatory elements, into one of chronicity, its composition being chiefly that of granulomatous tissue in which are embedded scattered areas of semi-liquefied polyhedral cells, remnants of the primarily affected squamous lining which are carried far down into the depths by the destructive exudates.

Meanwhile, the adjacent squamous lining is in contact with an inflammatory infiltration of a density distinct from that just discussed, yet possessing equal activity, since polymorphonuclear leucocytes are present in relatively equal quantity. The area now under consideration is, of course, the extreme edge of a zone of acute inflammation, the area at which tissue resistance is attempting to assert itself, or at which there is a falling off in the full force of the irritant. Irritation of the second degree, therefore, is a transient and relatively rapid phase between the destructive and milder types, and its action upon old squamous epithelium is observed only in connection with the active stage of true ulceration. It is the degree of non-destructive but most irritative type and is characterized by a typical reaction on the part of epithelial cells in contact with it. At either edge of a most active ulcer, the under surface of the adjacent squamous epithelium is in contact for a short distance with an inflammatory infiltration, of the same active nature as that which has destroyed a section of it, but of a density approximating to about one-third. The cellular reaction in this region is most intense. The basal columnar layer is irritated to such an extent that its most active degree of metaplasic activity is called forth. Long, sharp pointed downgrowths are quickly produced as the result. The central cells of these downgrowths are of the new polyhedral type (as previously described) resulting from division of the basal columnar cells, but the cells lining the sides are of the low cuboidal or columnar type, true basal cells. It is at the extreme point of the downgrowth that the greatest activity exists, and here a small localized bulging may be brought about. The columnar cells can here be seen in the state of active division, newly separated cells being extruded upward to the interior of the downgrowth. The true columnar character of these basal cells can well be made out in most cases, but such is

their activity at this region that the height of the lowermost cells is often considerably diminished. The transition from the columnar to the polyhedral type is well observed in the recently produced cells as they recede farther from the base. The tremendous activity of these basal cells acts as a protection to the central cells. Even in contact with this degree of irritation, the basal layer remains functionally intact. In the most irritated cell downgrowths a small abrasion of this layer may occasionally occur, with local cell destruction beneath, but that the external irritant does not tolerate irritative reaction on the part of the central cells, is shown by their lack of, or negligible, proliferation. Such a breech in this protective and functional layer is but a momentary in the case of epithelium, the reactive powers of which are capable, if only just, of combating the irritation inflicted upon them. This is so in the instance under consideration. In such a case the more acute stage of ulceration will be overcome and the condition will pass into chronicity and thence to healing.

Figure 24 shows the phenomenon here described. The type of cervix subject to ulceration is one that has undergone some previous hypertrophy. The squamous covering in this case is already thickened by the slow process of cell production under the lowest grade of irritative stimulus. The epithelial cells as a whole, however, may be said to be relatively old (although not as old as those comprising the original covering) on account of the extreme slowness with which this thickening has taken place and the length of time which it has been present. These facts are proved by the relative thickness of the superficial flattened cells of the stratum corneum, and the relative paucity of recently produced cells in the malpighian layer, which is almost entirely composed of vacuolated cells of the long standing type. The squamous covering shown in Figure 24, therefore, is of the type common in long standing hypertrophy. The basal columnar cells, therefore, are now functionally old cells. There is now no subepithelial rarefaction. Fibromuscular elements abut on to the epithelial. Regenerative vitality must have been acquired as the result of long continued rest. This type of epithelium then must be considered old.

It will be seen when old epithelium is in contact with an irritant, such as in this case, that the dense subepithelial fibromuscular tissues exert a protective effect of their own. The inflammatory cell exudate can be seen to occupy positions between the muscle bundles, which themselves serve as a partial barrier between this and the epithelium. There is obviously much greater difficulty in the irritant making contact with epithelial cells which are closely supported by dense mesoblastic structures than with those unprotected in this respect.

I consider that the importance of the cell reactions involved by contact with this grade of irritant lies more in the remote effect produced than in the immediate one. The immediate effect shows a great tribute to the manifold activities of the cells of the basal layer. The complete reaction is quite distinct from anything else seen in epithelial activity, and it is for this reason that I have nominated the causal agent to a degree of virulence of its own, namely, the second degree. The reaction is, however, a definitely localized one and, notwithstanding the angry nature of it, is not one of immediate danger, from the point of view of malignancy. This is the most rapidly produced epithelial reaction possible. The thinner and more pointed the downgrowths, the more rapidly they have grown, the greater the proportion of proliferative to metaplasic activity on the part of the basal layer. There is no danger of malignancy at this stage. If a point is reached at which the basal cells fail temporarily or permanently in their function, a breech is made in this layer and the central cells are locally destroyed. There is little or no reaction on their part. The irritant in contact is of too active a nature to permit of irritative proliferation in cells of the passive type. The importance of this phase lies in its remote effect. The most active new cell production is combined with an extensive subepithelial rarefaction. At the close of this phase, one is left with the most highly sensitive epithelium possible, composed both in the basal and

other layers of very young cells and totally unprotected from below by supporting mesoblastic structures.

The effects of irritants of the first, second, and third degree of virulence upon old epithelium are the effects of different degrees of the same type of inflammatory reaction, namely, acute inflammation as evidenced by the polymorphonuclear character of the exudate. The three degrees differ only in the density of the infiltration. The three reactions are distinct. The type of irritant is, however, the same and its function, in sufficient concentration, is to destroy epithelium. This it does in the first degree but not in the second or third. An irritant of the first degree nearly always attacks the epithelium from the surface aspect and it is as one of the second degree that its effect upon subepithelial contact is observed, thus resulting in the reaction just described. However, proof of the consequent destruction which would result from an increase in the virulence of a subepithelial irritant is shown by a study of Figure 25. According to my series, this is the rare condition in which an acute inflammatory exudate corresponding to the density of the first degrees of virulence is in contact with the squamous epithelium from below and along a wide area. The old nature of the epithelium can be observed as well as the strength of the deep supporting tissues. There is rarefaction, however, in the more superficial zones. The inflammatory infiltration is extremely dense and highly polymorphonuclear. It is obvious here that the cell reaction similar to that provoked by an irritant of the second degree has taken place, leaving rarefied areas between the downgrowths, and that the irritant has then increased in virulence to the first degree, either by addition to it or by diminution of the patient's resistance at this stage. The types of the cell downgrowths are now densely involved in inflammatory exudate, the elements of which can be seen to have penetrated through the basal cell layer into the substance of the central cells themselves. The muscular supporting elements in this region are, however, quite in evidence, but are not capable of adequate protection against this irritant. The terminal portions of the cell downgrowths are seen to be undergoing destruction by liquefaction. There is little or no irritative proliferative reaction on the part of the passive cells. Higher up in the rarefied areas, where the infiltration in contact is relatively slight, there are local metaplasic and proliferative reactions of a typical nature on the part of the basal columnar cells involved. The true destructive effect of an acute inflammatory infiltration is demonstrated here. There is no time for pure cell proliferation. Presumably the liquefactive properties of the polymorphonuclear leucocytes take effect too quickly. The very acuteness of the inflammatory reaction is a safeguard against malignancy, so long as the acuteness lasts. As I have said above, irritants of the first, second, and third degrees of virulence belong to this type.

THE EFFECT OF THE ACTION OF AN IRRITANT OF THE THIRD DEGREE OF VIRULENCE UPON OLD SQUAMOUS EPITHELIUM

The production of bulbous downgrowths. Without doubt the most common of the cell reactions observed in connection with epithelial irritation affecting the squamous layer is that produced by irritants of the third degree of virulence. It is the reaction typically resulting from the effects of an irritant of moderate strength acting over a longer period than those just discussed. It is to be found in the regions more remote from the zone of acute destruction in so called erosions and commonly as a phase during the stages of healing. It is also seen in the more chronic or less active type of ulceration. The bulbous or blunt epithelial downgrowth is the direct outcome of the effects of an irritant insufficient to cause destruction, but of sufficient strength to stimulate the basal layer to active metaplasic and proliferative activity of a slower and more uniform nature than that observed in the case of the second degree. The rate at which cell activity is called for is such as to enable the cells of the basal columnar layer to react more constantly and, as a rule, in degrees varying directly as their distance from the apex of the downgrowth, which point owes its position to a localized

increased concentration of the inflammatory reaction concerned. The infiltration produced by this particular degree of irritation is of a density distinct from that of those already discussed and approximates to half that of the second degree.

In the case of the third degree, however, a certain latitude is allowable as to the actual density of the infiltration, and the bulbous downgrowths produced vary somewhat in the degree of bluntness directly as the degree of this density. This variation, however, in no wise detracts from the definite character of the third degree as a whole, as evinced by the specific cell reactions called forth by its action. It is also distinct in every way from the preceding and proceeding degrees of irritation.

The inflammatory infiltration in question is produced on the outer zone of a focus of acute inflammation. A point is reached at which the infiltration is reduced to a stage of easy tolerance on the part of the tissues in contact with it. This process is of course gradual, the diminution in the density occurring uniformly in conjunction with the distance from the central focus. After the zone occupied by the second degree is passed, however, the irritant no longer possesses the power of destruction, and from that point down to one at which the acuteness of the reaction may be said to cease, a typical cell response is produced resulting in the formation of bulbous downgrowths, as aforementioned, which differ only in their length and bluntness according to the slight variations in the density of the infiltration which has been in contact.

Figure 27 shows an example of the more active type of bulbous downgrowth. This type, of course, is found in connection with the outer zones of active ulceration or nearer to the central zone in the case of the more chronic ulcers or healing ulcers.

It is a fact, as is natural to suppose, that the long bulbous downgrowth does not occur in connection with acute erosion as the process is far too transient to allow of their production.

A long continued irritation in contact with the basal layer of the epithelium is necessary to the production of this type, and this can be affected only in conjunction with true ulceration (Cf. ulcers).

In Figure 27 this condition may be observed. The original squamous layer shows a condition of long standing hypertrophy. The relatively newly produced cells stain more deeply in the region of the base of the downgrowths. As they recede to the surface, the nuclear staining becomes fainter until it is gradually lost as they approach the surface. New cell production is seen to be carried out at the sides of the downgrowths in the same way, but not to quite the same extent, so that the bulbous shape is thus maintained. The depth of the newly produced cells is relatively slight, as compared with the mass of old ones, thus demonstrating the slowness of the general reaction. The inflammatory infiltration is observed to be uniform but mild as compared with that observed in the preceding degrees. Exudative cells are seen in contact with the downgrowths both at the sides and bases, and it is obvious that the relative rate of cell production by the basal layer varies as the density of the infiltration in contact. The subjacent fibromuscular elements are observed in normal density and are acting as a partial protective agent to the epithelial cells, as previously described. Of course, these bulbous downgrowths may assume great relative size, varying with the length of irritation experienced and the degree of resistance of the subjacent tissues. A large bulbous downgrowth, for instance, is likely to result from active epithelium situated at the mouth of a cervical gland. The new cells easily fill the gland lumen. Figure 28 shows an example of this. But, in all, the process is the same—that of steady, uniform, polyhedral cell production by metaplasic activity of the basal layer, combined in addition with constant proliferative activity on the part of these same cells.

The bulbous downgrowths seen in connection with transient erosions are generally of a more uniform type and smaller. They are the result of a much less prolonged irritation. Figure 29 gives a fair example of this type. In this figure the columnar character of the basal layer is well shown. The newly formed

polyhedral cells can also be seen being extruded toward the epithelial surface. The regular subepithelial infiltration is well observed.

Figure 30 shows another example of squamous cells in process of filling a proliferated gland space. It will be seen that the production of cells is from the sides of the downgrowths, which are in contact with the irritant, and that old polyhedral cells are being forced down by pressure into the gland lumen. There is no cell activity at the base of such a downgrowth.

Numerous examples of bulbous downgrowths may be observed in connection with inflammatory conditions of the cervix. The foregoing are typical examples. The depth of the downgrowth varies as the length of the irritation and the degree of resistance by subjacent tissues. The longest downgrowths are, therefore, observed in connection with the outer zone in chronic ulceration and in cases in which the cells are placed within a gland lumen which contains an inflammatory exudate. In certain cases the irregular shape of the downgrowths, together with artefact in preparation, give a pseudo appearance of early malignancy. Figure 31 shows an example of this. A few irregularly shaped downgrowths, with small areas apparently separated owing to prolongations having been cut across, present an appearance which might be mistaken for commencing malignancy by anyone not accustomed to gynecological pathology.

In all this type of case, however, it will be seen that an acute inflammatory exudate of a certain maximum density, approximating to half that observed in the second degree, is in contact with the basal layer, that new cell production takes place from this layer on all sides of the downgrowth, and that the rate of production varies directly as the local density of the general infiltration. The fact is evident, however, that the rate of new cell production called for by this third degree of irritation is not too fast to be conveniently dealt with by the metaplasic and proliferative powers of the basal layer of cells. In no area does one find a rupture of this layer with destruction of the polyhedral cells beneath. Here and there along the edge of the downgrowth, localized increased activity is seen, but this is accompanied by adequate replacement by the basal layer, and a new bulging prolongation results. The type of cell reaction to this degree of irritant is definite. Whenever a looser subepithelial infiltration of the same nature is observed, it is merely a transient prolongation from one of this degree, and as such is not responsible for any specific reaction.

Figure 32 shows very well the effect of this degree of irritant upon an old, thickened epithelium. The squamous covering here has long ago passed through proliferative activity, so much so that its entire thickness is practically made up of vacuolated cells possessing little or no cytoplasm. In these cases of long standing hypertrophy, as before mentioned, one looks upon the epithelium concerned as relatively old.

An irritation supervenes here and one can observe the zones of newly formed polyhedral cells standing out by contrast of their cytoplasmic contents from the old squamous cells. The basal cell activity and subepithelial infiltration are well shown. The general reaction results in the production of irregular bulbous downgrowths.

Figure 33 again shows a good example of the bulbous type of downgrowth extending over a wide area.

With a consideration of the third degree of irritation, we conclude the question of the effect of acute inflammatory infiltrations upon old squamous epithelium. I find that the effect of the purely chronic type of inflammatory reaction falls into two closely approximated types, which nevertheless might be distinguished on account of a difference in density. The first, or more virulent of these, we will now consider under the heading of the fourth degree.

THE EFFECT OF THE ACTION OF AN IRRITANT OF THE FOURTH DEGREE OF VIRULENCE UPON OLD SQUAMOUS EPITHELIUM

Chronic inflammation. The purely chronic type of inflammatory subepithelial exudate is comparatively rare. There is no doubt that in my series this particular reaction occurs only once, approximately to every thirty

examples of the acute variety. The cell reaction produced is negligible. There is very little irritative quality associated with a pure round cell infiltration. This type, however, is worthy of note on account of the well known pathological regard for "chronic inflammation" and "chronic irritation." These, of course, are terms loosely applied to inflammation and irritation of long standing and do not necessarily apply to this exact type, which, as we shall see in connection with the cervix uteri at any rate, is a factor of relatively little importance.

Pathologically the effects of the purely chronic form of irritation, as evinced by the presence of a purely round cell subepithelial infiltration, are small in comparison with those just discussed. They should, however, be divided into two degrees according to virulence. The denser form, that which forms the subject of this chapter, is observed as a fairly regular infiltration in contact with the basal layer of the epithelial covering, having a density less than that associated with the active infiltration of the third degree, but possessing irregularly scattered nodes of concentration, similar to the lymphatic nodes observed in cases of leucoplakia vulvæ.

I do not consider these to be of the same nature inasmuch as they are more intimately connected, as a rule, with the general infiltration. I regard them nevertheless as an evidence of the relative virulence of this type of irritation, such as it is, and estimate that a reaction of this character possesses an irritative power only one stage less than that described as the third degree.

The typical reaction observed is distinct from all others in so far as the general cell activity is concerned. The epithelial response is limited and stunted. The mesoblastic tissues show little or no change. The basal columnar cells react to the irritant irregularly and to a relatively limited degree. Irregular, short, and scattered cell downgrowths are produced. Small nodular protruberances form the epithelial base rather than downgrowths. The slowness with which they are produced is evidenced by the fact that the cytoplasmic staining faculty of the more recently formed polyhedral cells differs but slightly from that of the older cells in the epithelium; and that the number of newly formed cells, even in respect of the areas of downgrowth, is small, a fact which is demonstrated by the relative narrowness of the more deeply staining zone of new cells.

Where the infiltration is somewhat diminished, an irregularly diffuse thickening of the epithelium is produced by more regular basal cell activity. The fibromuscular elements remain practically unchanged. There is no rarefaction.

Figure 34 shows this reaction and indicates the position of a localized area of concentration in the infiltration.

The epithelial reaction here agrees in detail with what one would theoretically expect by a comparison with the effect of an irritant of the third degree. There is no doubt that the squamous epithelium behaves uniformly toward external stimuli. This uniformity of behavior is a constant factor throughout. The squamous epithelium itself holds no secret.

THE EFFECT OF THE ACTION OF AN IRRITANT OF THE FIFTH DEGREE OF VIRULENCE UPON OLD SQUAMOUS EPITHELIUM

The irritant of the fifth degree is the mildest possible one and is represented by the presence of a loose, round cell infiltration in contact with the basal layer of the epithelium, of a density approximating to one half of that associated with the fourth degree.

As might be expected from the uniform and slight nature of the stimulus (there are no associated points of concentration of the infiltration), the epithelial reaction is also uniform, or nearly so, and this takes the form of a generalized thickening by new cell production from the basal layer. There are no localized cell downgrowths here because the irritant never reaches a sufficient concentration to force their production. However, wherever the density is slightly increased, one may readily observe a corresponding slight increase in the general epithelial thickness, another tribute to the extreme uniformity of the epithelial behavior. It is certainly in these lowest grades of irritation that one may

perceive the true delicacy of the epithelial cell reaction. Moreover it is from a study of this type of reaction as a basis that one may come to understand the cellular upheavals associated with the grosser irritants.

Figure 35 shows an example of the reaction to this degree of irritation. Beneath the somewhat thicker epithelial covering, the lymphocytic infiltration is seen to be slightly denser. The metaplasic activity of the basal cells, which are here well seen to be of a definite columnar type, is observed to be slightly greater in connection with the slightly denser zone of infiltration. The distinction is slight, but definite, and undoubtedly proves the delicacy and uniformity of cellular response to irritation.

Under the high power one may once again observe the specific metaplasic function of the basal columnar cells. The process of cell and nuclear division may be seen—an elongated cell containing two nuclei, the upper half of this cell being destined for the passive protective rôle of the polyhedral type (Fig. 36).

With the consideration of this lowest degree of irritation, we complete the study of the effects of irritation generally upon old squamous epithelium. The five main degrees into which irritants have been divided are based, as previously explained, upon the constancy of the associated factors in each, viz.: (1) the density of the inflammatory infiltration produced by the irritant and (2) the cellular reaction invoked. The histological picture in each case is constant.

THE CANCER PHASE—ITS RECOGNITION WITH REGARD TO SQUAMOUS EPITHELIUM, AND THE EFFECT OF AN IRRITANT OF THE THIRD DEGREE OF VIRULENCE UPON NEW SQUAMOUS EPITHELIUM

In the foregoing text I have attempted to stress two points particularly: (1) the delicacy and constancy of epithelial cell behavior under varying conditions, and (2) the histological and physiological distinctions between old and new squamous epithelium and columnar epithelium.

To my mind, from the examination of this series, the epithelial response to an obvious stimulus in all its varying degrees is so constant a thing that one can not for a moment credit the possibility of behavior other than constant, under any other circumstances or set of circumstances, on the part of these cells which have been only too ready to disclose their methods of weathering the mildest and severest storms of irritation.

Should it not be very probable then, that the very inception of cancer change in these same cells is the result of a similarly constant phenomenon?

It remains to acquire and study examples of the very earliest evidences of malignancy in the cervix, so early that histologically it has hitherto been impossible to recognize them as such.

The cervix removed for malignancy is, of course, useless in this respect, the condition being too advanced histologically, but in a long series of cases such as now under consideration, examples of the beginnings of cancer may be found. Even then, however, slight as may be the evidence, the very definite character of it may be sufficient to mark the mode of its inception. It is not sufficient to say, "This epithelium has gone to the length of cancer change." The phases immediately preceding that change must be recognized—the Cancer Phase. The reason for something distinct from the cell reactions hitherto discussed, which are associated with varying stages of cervicitis and ulceration, must be elucidated. We now thoroughly understand the pathology of erosion and ulceration as also the minute reactions of the epithelia involved in these conditions. We have accepted the fact that these states are predisposing factors to cancer growth. All pathological evidence has been overwhelmingly in favor of this being the case. My pathological findings in this series support this fact.

The stepping stone between the benign and malignant must be found—the link between cervicitis (erosion) and cervical cancer.

We have previously discussed the question of the relative age of the cellular elements composing the squamous covering (Part 2, par. 1) and have recognized the distinction

between old squamous epithelium and that which has been recently formed as the result of the reparative mechanism in dealing with the damage caused by cervicitis. The new squamous covering is always found, therefore, in conjunction with evidences of the end-results of cervicitis: proliferation of the cervical glands in the region of the external os, distended gland spaces in this situation, and a certain amount of rarefaction of the subjacent mesoblastic tissues. The new epithelium itself is often fairly uniform in thickness. The cells composing it are very much more uniform in their staining properties than those concerned in old squamous epithelium. As a result the basal columnar layer is not so prominent, and in addition the cells comprising it are a little more inclined to the cuboidal on account of their recent productive activity. The nuclei of even the surface cells are still obvious, there being a relatively narrow layer of the more flattened type and these but partially flattened as yet. The entire cell content of this recently formed structure is young. The diffuse and deep cytoplasmic staining together with the large size of the cell nuclei indicate this fact. The newly produced polyhedral cells are of necessity highly unstable, not far removed from the embryonic at this stage. Until they have enjoyed immunity from external irritation for a certain minimum period, as the result of complete protection by the basal layer which produced them, they will not acquire that histological proof of stability indicated by the gradual loss of cytoplasmic staining and the diminution in the size of the nucleus, which is observed in their older counterpart and which is known to be the associate of complete passivity both in function and in responsiveness. These new cells have the same passive rôle to play if they are allowed to grow old enough to play it. The cells of the superficial zone are nucleated, having been rapidly extruded to the surface in the manufacture of the new covering. The basal columnar cells must necessarily be relatively unstable as such, having been called upon to exert their full metaplasic function in this production. As pure protecting cells they cannot be compared with the basal cell layer seen in old and hitherto unaffected epithelium, nor even that associated with a diffusely (and hence slowly) thickened epithelium resulting from the effects of low grade irritation. In these latter cases we have seen how the basal layer reacts to the varying degrees of external stimulus, but in the case of newly produced epithelium the complete destruction of this layer is much more easily accomplished, and even the destruction of the new epithelium itself. As I have said elsewhere, however, destruction of epithelium is a safeguard against malignancy. Irritation of epithelium short of the power to destroy is the danger; and especially is this the case where the young cell is the one affected; and more especially still when that young cell plays a purely passive rôle functionally and can react to stimulation only by active proliferation. If that young cell were allowed to age only sufficiently to lose the active elements of its protoplasmic and nuclear contents, as evinced by the deep diffuse staining properties of these constituents, and to pass into its functional and responsive inactivity, the resultant reaction to external irritation would be nil or practically so, as shown by the effect of destructive irritants upon old squamous epithelia. In all our previous inquiry, the basal layer has either been in a position adequately to protect its inactive progeny or this has been destroyed with little or no reaction along with the basal layer.

In a word, there are only two conditions under which an irritant can exert prolonged action upon the polyhedral cells of squamous epithelium without being strong enough to destroy them. In every other case the basal cell layer is strong enough to protect them by metaplasic activity. Penetration of this layer by destruction results in destruction of the less resistant polyhedral cells beneath, *ipso facto*. It remains, therefore, for the basal layer to weaken itself out of proportion to the maximum resistance of the cells it has produced. This is the state of affairs in the case of (1) entirely new squamous epithelium, such as we have just discussed, and (2) old squamous epithelium which has undergone rapid and continued activity as the result of

irritation, a condition of things observed in connection with ulceration. In this latter case, however, the resultant columnar and polyhedral cells produced are relatively more resistant and stable than those of entirely new epithelium—in so far as they have been produced by a regular, if rapid, metaplasic activity on the part of basically old and original columnar cells, in contradistinction to a new cell production from a basal layer which itself owes its presence to proliferation.

However, there is no doubt that this latter condition does present that proportional diminution in protective strength to the basal layer necessary to the inception of cancer, but, as I have stated, not in so marked a degree as in the former state; and we shall see that it is the new epithelium therefore which provides the most favorable basis for cancer growth.

Figure 37 is derived from a cervix which was removed during the routine operation for prolapse. The cervix was somewhat hypertrophied and exhibited the gross appearances associated with old erosion: a chronic catarrhal exudate, the presence of nabothian follicles, and so on.

Histological examination of this cervix, however, discloses a relatively small area of the portio, near to the external os, which shows evidence of a recently recovered erosion. The new epithelium is of more or less uniform thickness. The cells composing it stain fairly deeply throughout. Their nuclei are relatively prominent by reason of their size and deep staining property. The contents of these cells possess in the greatest degrees those qualities which are the birthright of the infant cell—that cell which is newly produced by the very specific activity of an older type; produced as the result of metaplasia. The cell contents show plainly the ease with which such a cell could respond to external stimulus by proliferative multiplication in the effort to reproduce its kind; an activity which must inevitably lead to the gradual retrogression of the type.

It is evident that these newly produced cells possess, for a time, an excess of the normal constituents—a protective measure against absolute extinction at birth—which is quickly absorbed as the cell proceeds to its passive function, receiving its protection thenceforward from more recently produced cells of the same kind, if not from the basal layer itself. It is a fact that the cytoplasm and nucleus diminish in bulk and character (as evinced by the diminution in basic staining property), as the cell is extruded to the surface, that is, as it becomes older, as it recedes farther from the possibility of external stimulation, and as it becomes progressively more and more passive functionally. I cannot say that these cells, at birth, possess for a time by derivation, something of the specific metaplasic function of their forbears, except in so far as their obvious preparation for activity is concerned. The cells produced by them are of the same type though rapidly proceeding to the parasitic or malignant.

In the section under consideration, the cells even of the superficial layers show well marked nuclei. There is no horny layer of flattened, empty cells as yet. The basal layer is well seen and the columnar nature of its cells can be observed. There is a certain rarefaction of the subepithelial tissues, relatively wide spaces intervening between faintly staining muscle elements. There is no evidence in this case of hyaline deposit, but this occurs in varying degree in certain other cases. I attach no great importance, however, to this factor as it in no wise affects the point at issue. I consider hyaline deposition as an occasional associated factor in subepithelial rarefaction. Proliferated and distended cervical gland spaces are present in this section and encroach to the edge of the area under examination. The whole is a picture of a recently recovered eroded zone. How recent one can only guess.

Beneath, and in contact with this new epithelium, is an acute inflammatory exudate, of marked polymorphonuclear character, but in no way differing from exudates of equal density observed heretofore. This exudate corresponds to that which is produced by an irritant of the third degree of virulence. Its density is not great. The cellular exudate is moderately scattered, but the rarefaction of

the tissues in which it is situated readily enable these inflammatory cells to form actual contact with the new basal layer. This fact can be observed. Localized zones are seen in which the columnar cells of the basal layer are responding nobly to this unforeseen irritation and are reacting in truly typical style. The actual cell and nuclear division can be seen even under the low power. (This fact furnishes yet another proof of the nature and formation of these cells.) The under surface of the epithelium therefore bulges downward in very slight degree here and there. The irritation is obviously of very short standing as yet. The metaplasic activity of the basal cells has only just begun.

In other areas, however, it can be definitely observed that the inflammatory cells have broken through the basal layer and are in actual contact with the most recently produced polyhedral cells. The basal layer has failed at last in its protective function. Its continued and prolonged activity has weakened it out of proportion to the maximum powers of resistance of the cells it has just produced. One can make out the scattered and macerated cells of this layer in the general exudate.

The reaction on the part of the subjacent cells is that for the observation of which we have conducted this search.

In this particular case the reaction is just commencing and has only proceeded to the extent of relatively slight increase in cell formation. It is, however, definite. There is a generalized loss of cell outline due to a general protoplasmic diffusion through the cell walls. There is a generalized lack of cell individuality. Overdistention of existing cells by deeply staining cytoplasm is noted. There is loss of cell shape, possibly by bursting. Already irregular shaped and mitotic nuclei can be seen. Large diffuse nuclei shade off into the surrounding cytoplasm.

The whole affected cell mass is blurred and ill defined. There is multiplication by proliferation. The depth of the epithelium is increased. The newly formed polyhedral cells, temporarily possessing in high degree the wherewithal to reproduce their kind, are proliferating actively under stimulation, and at the expense of their own existence. Each new cell produced in this way and at this speed from a newly born (by metaplasia) cell as a base, must inevitably possess less of the characters vital to functional life than its predecessor. The exact nature of these characters does not concern us in this investigation. Enough has been written upon the subject of cell morphology in cancer to make this clear. My object is concerned solely with the recognition of the onset of this change and I believe that here, in this specimen under examination, one may perceive the earliest evidence of the incidence of cancer in the human subject.

Figure 38 shows a view of the temporary and spasmodic metaplasic activity of parts of the basal layer and also the appearance which I have described as typifying the earliest onset of cancer change. The relatively loose nature of the subepithelial infiltration, corresponding to the third degree, is seen. The atypical nature and shape of both cells and nuclei, together with the protoplasmic diffusion which results in a blurring of the affected cell mass is also observed. There is a slight increase in cell depth of the epithelium caused by the new cell production. With regard to squamous epithelium, this is the moment of change from benign to malignant—the Cancer Phase. In every way, notwithstanding the slight degree of change from the normal here produced, the histological picture conforms in detail to that present in developed cancer.

In the case under observation the subepithelial infiltration, which has brought about the specific changes just discussed, shows areas of increased density in two or three separate and distinct regions. The squamous epithelium in contact with these areas, which correspond to an irritant of the first degree of virulence, is locally destroyed with little or no reactive change, thus agreeing accurately with the behavior of old squamous epithelium in contact with a similar irritant. Figure 39 shows this phenomenon. The complete absence of cell reaction is noticed, the picture being one of rapid destruction. Naturally one expects

this to be the case, the new squamous epithelium being less resistant in all respects than the old. It is, however, all important to observe, in the one case, the two cell reactions toward two degrees of irritation, and to compare these with those occurring in the case of old epithelium. The effect of the irritant of the first degree must necessarily be the same in each case, but that of the third degree depends upon the type of squamous epithelium involved, the cancer phase being the outcome of the effect of an irritant of the third degree upon what we now recognize to be new epithelium.

Figure 40 shows a somewhat farther advanced stage of this phase. In this specimen one may recognize the junction between the old squamous covering and the newer epithelium which has recovered an old eroded zone. The widespread subepithelial rarefaction which is present in conjunction with the line of new epithelium, which proceeds down to the region of the cervical glands, is typical. The type of new epithelium is also typical, the general thickness being in this case uniform, except where now obliterated or stimulated, and the cells composing it more nearly approximating to one another as regards age than those of old epithelium. Here in this specimen, however, there has obviously occurred a recurrence of epithelial irritation, which is affecting this newly healed area, and this is evidenced by the presence of an acute subepithelial inflammatory exudate in contact. This exudate varies in density in parts of the affected area. Where it approximates to an irritant of the first degree, the epithelium in contact is destroyed wholesale without reaction. This is the case over a relatively large area in this specimen. When the density of the infiltration corresponds to an irritant of the third degree, the typical epithelial reaction is produced. In this case one may observe the contact made between the exudate cells and the polyhedral cells of the epithelium. It is possible to see small groups of faintly staining basal columnar cells scattered by desquamation but still in the region of their normal position. They are no longer functioning. Masses of irregularly shaped cells are locally produced by proliferation from the activity of polyhedral cells. The most recently produced are often grossly enlarged and engorged by their cytoplasm. Their nucleus is large and diffuse. There is no longer any base line to the squamous epithelium. Irregular perforations of it have taken place and irregular cell masses composed of infant cells, many indistinguishable from the malignant, are beginning to penetrate into the rarefied tissues beneath. In other parts the basal cells are seen to be still functioning, but it is obvious that the rate of activity is great. The type of polyhedral cell produced is not normal. It is too large, too distended, too deeply staining. Its nucleus is too diffuse. In some cases nuclear division can be seen. The cell produced is too primitive. However, where metaplasic activity has for a time prevailed, epithelial downgrowths of varying degree are formed. They are nevertheless quite distinct from those brought about by the activity of old epithelium.

It is but a trivial step from the phase which we have just observed to that of developed cancer. Differences hardly perceptible would lead to a definite assertion as to the presence of cancer. There is no doubt that the rate of cell activity in the phase just observed is even increasing. Each new cell produced is more active from a proliferative point of view than its predecessor. Soon the picture will be dominated by typical cancerous activity. This crucial phase will be obliterated. The vast majority of specimens examined are typical and hence useless from our point of view. The onset of developed cancer is associated with an increase in the density of the inflammatory reaction in contact. This is only to be expected since a relatively large area is involved by the presence of foreign cells. Also the secondary infection by pathogenic organisms is immediate once access is obtained, and this is simple in surface cancers.

Figure 41 shows another instance of this vital phase. Here a subepithelial inflammatory exudate approximating in density to the third degree has destroyed the basal layer and, by affecting the polyhedral cells directly, has produced atypical downgrowths consisting of typical primitive cells. The dis-

tinction between these cell masses and those produced as the result of the activity of old epithelium is distinct. In reviewing this long series, the various distinctions in cell morphology are evidenced time and again. There is no distinction, however, so definite as that which exists between a collection of infant cells, such as occurs in the production of this phase, and all other types.

Yet another instance, and this somewhat more advanced still, can be observed in Figure 42. Here the new epithelium has produced atypical downgrowths of the type described over a minute area. The subepithelial infiltration in contact, which is responsible, is very typical and the method of production of these downgrowths from the new polyhedral cells corresponds to that already described. Here is a case which exhibits an area, totally included within the field of the low power of the microscope, which is passing through the interstage between the benign and malignant. The same may be said of the case from which Figure 41 is taken. In the case from which Figure 40 is taken a greater length of epithelium is involved but this is because the process of healing has of necessity involved a larger area.

The production of the cancer phase with regard to squamous epithelium, therefore, results from the effects of an irritant corresponding to the third degree of virulence, acting in contact with the under surface of relatively new epithelium. It is, of course, impossible to say for what length of time this action must be maintained in order to produce this result. By comparison, it appears to me to be quickly produced. The important point is that the infiltration is not in sufficient concentration to destroy utterly. Only the attenuated basal layer is destroyed. Moreover, the attack is delivered from below. There is every facility for the production of a subepithelial inflammatory reaction by direct spread throughout the rarefied supporting tissues, but whether or not this is the case I am not prepared to say. Possibly the irritant is conveyed by the blood stream in this instance. However, it is necessary for a distinct recurrence of the irritation to occur in a subepithelial situation and during the time of instability of the epithelium. Undoubtedly the cancer phase reactions described are progressive from this point. There is no doubt that these reactions must increase rapidly with each new cell produced. Moreover, as the mass of infant cells becomes larger and consequently more parasitic in type, the infiltration in contact will increase in density both by reason of the presence of an increasing "foreign" element, and of the fact of increasing tissue activity and also on account of the increasing ease of secondary involvement by septic organisms as the result of progressive surface softening in the affected area. We, therefore, see in cases of developed cancer an associated inflammatory reaction which approximates more nearly to the first degree of virulence; but we must remember that this was not the one concerned in the initial production.

Figure 43 shows one of the earliest evidences of developed squamous cancer that I have in my series. The whole affected zone can be included in the low power field. I consider, however, that the cell morphology is typical. The area involved corresponds to that of an erstwhile healed erosion. Proliferated cervical gland spaces can be seen beneath this minute cancer. The general softening, which affects the surface, can be observed and the localized dense inflammatory infiltration which surrounds the involved epithelium is undoubtedly partly derived from bacterial infection through the surface. The junction with the more normal epithelium is abrupt because of the difference in density of the adjacent tissues causing separation on cutting. Yet the distinction between the cell reaction here and that seen and described in the preceding cases is barely discernible. The transition takes place insensibly and is now complete. Figure 44 shows the high power view at the junction of the normal epithelium.

I feel that the link between the benign and malignant is bridged by the full consideration of the cases concerned in Figures 37 to 43. There is no doubt in my mind as to the mode of transition, and I trust that this has now been made clear.

I have previously explained that the activity of the basal layer in true ulceration may be such as to weaken locally and temporarily its component cells out of proportion to the maximum power of resistance of the polyhedral cells which it has produced; but that this is not nearly so probable as in the case of entirely new epithelium which owes its existence to recent manufacture by basal cells themselves produced by great proliferation.

Moreover, in the case of true ulceration there is not that transient phase of quiet which allows of the devitalizing specific metaplasic activity of the basal layer. The cellular downgrowths occasioned by active ulceration are controlled for the most part, as already explained, and if, as rarely is the case, but as Figures 25 and 26 show, there occurs a temporary increase in the virulence of the irritant in contact with these downgrowths, the new polyhedral cells are destroyed without reaction along with the cells of the basal layer. The irritant in contact is too strong to destroy the basal cells and stimulate the polyhedral cell without destruction. For this reason the true ulcer is much less liable to malignancy than the proliferative erosion. As I have said previously, cell destruction is a safeguard against malignancy.

In this respect, therefore, it would be necessary for the adjacent epithelium of a long standing ulcer, one which has passed the active stage, to be re-stimulated by an irritant corresponding to the third degree of virulence; and this to be done in connection with prolonged downgrowths which have taxed the proliferative and metaplasic powers of the basal cells to the full, and before recuperation on their part has been effected. It would then be possible, but not as probable as in the case of new epithelium, that the basal layer cells in the region of the apices of the downgrowths, that is, the most recently produced, might be locally destroyed, thus allowing direct contact between the irritant and the subjacent polyhedral cells. It is a clinical fact that the development of cancer in connection with ulcers takes place in the long standing chronic type, such as we have observed in this series, and not in the truly active ulcer.

THE CANCER PHASE—ITS RECOGNITION WITH REGARD TO COLUMNAR EPITHELIUM AND THE EFFECT OF AN IRRITANT OF THE FIRST DEGREE OF VIRULENCE UPON NEW COLUMNAR EPITHELIUM

In the chapter dealing with the relative age and function of columnar and squamous cells, I have indicated the extreme distinction which exists in the matter of resistance to irritative stimulus between these two types. The columnar epithelium of the cervical glands is extraordinarily resistant to maceration. This fact has been shown in dealing with the proliferative activity of these cells in response to stimulation by an irritant which is sufficient to destroy with ease, and without reaction, the squamous epithelium. The columnar cells of the basal layer of the squamous epithelium, we have seen to possess a degree of resistance relative to their specific function, but in so far as they are a smaller type and functionally much more active, their resistance cannot be nearly so great as that possessed by the large, relatively empty and thick walled cells the function of which is largely of a secreting nature, and not in any way connected with new cell production.

I regard these columnar cells, which line the normal non-proliferated glands of the cervical canal, as practically immune from malignant change. Cell change in them occurs only as a response to the most prolonged and virulent form of irritation. Their normal reaction, as we have seen, is by direct proliferation and new gland formation. The cells lining the old gland spaces for the most part remain unchanged.

Even gland proliferation, of definite degree, is not provoked by irritants of less than the first degree of virulence. We have seen elsewhere instances of the resisting power of these older gland spaces to irritants of the lesser degrees. When, however, the irritant in contact is prolonged in action and of extreme virulence, certainly of the first degree, columnar cells very occasionally show a direct reaction by the local production within the gland space of typical large polyhedral

cells, morphologically similar to those produced by the columnar cells of the squamous basal layer. Prolonged stimulation of these cells, therefore, results in the production from them of a different type of cell, a process of delayed metaplasia analogous to but much less easily provoked than that seen in connection with the basal squamous layer. In other cases they may react by sudden and irregular gland multiplication, a process which proceeds directly to the malignant. Both these reactions, where truly original gland elements are concerned, are extremely rare. With regard to the former reaction, there is always some associated gland proliferation, which occurs in the presence of irritation, *ipso facto*, so that one may practically assert that direct cell change does not occur from original gland epithelium.

Indeed, it is only in the relatively rare cases of localized acute intracervical irritation, which occurs in the absence of surface erosion, that the original gland epithelium is affected in this way. In the vast majority of cases surface irritation involving the squamous epithelium is present, and in these the deeply placed gland elements show no cell reaction. It is left, therefore, to the newer gland elements, those resulting from direct proliferation in cases of surface irritation, to exhibit that type of change which proceeds inevitably to the malignant.

Figure 45 gives a good instance of the tremendous resistance of this type of epithelium. Here recently produced glandular elements are surrounded by an inflammatory infiltration of great density—equal to the first degree of irritative virulence. Little or no reaction results, however, in the cells themselves. The inflammatory exudate does not penetrate the basement membrane—which I consider to be extremely resistant—and the glandular epithelial cells are, therefore, out of actual contact with this exudate. I believe that this fact plays the same important part in the production of individual cell stimulation with resultant change, that has been seen in the case of squamous epithelium. Figure 45 merely emphasizes a point that we have observed in many previous instances during our routine study of this series.

Occasionally localized cell downgrowths of minor degree are seen to originate from isolated areas of the surface epithelium of the canal. For the most part these are due to the stimulation of isolated prolongations of the squamous epithelium. Small strips of this epithelium occasionally encroach beyond the normal squamous-columnar junction and remain as minute surface patches on the surface of the canal. I have not attached any special importance to these areas and have always found the epithelium concerned in them to react identically with adjacent and more normally situated epithelium of the same kind. In this connection I do not necessarily agree with Moench and other authors as to the excessively sensitive nature of squamous epithelium in this region. Although its presence has been frequently demonstrated in my cases, there has never been any definite evidence of untoward activity associated with it. Neither, indeed, would I expect such to be the case, in view of the normal morphology of its constituent cellular elements.

The new glandular elements, rapidly produced by proliferation, however, cannot possibly possess the resistance of their parent cells. It is in connection with these that we see the eventual degeneration of the glandular epithelium by enforced individual cell multiplication. There is no doubt that the high columnar cells which line the new gland spaces in the region of the surface erosion, though morphologically similar, are much less adult than those from which they have originated. If proliferative activity has been rapid, there must be many of these cells which possess little or no further activity in this respect. The normal reaction to irritation is exhausted, just as it eventually is in the case of the basal layer cells of squamous epithelium. Further stimulation results in the direct production from these cells of polyhedral type cells, as the result of a metaplasic activity analogous to that possessed by basal columnar cells. Whereas, however, in the case of basal columnar cells, this process can proceed at length by virtue of the specific function of these cells; in the case of these attenuated columnar gland cells this reaction marks their ultimate

response to the contact irritant and results in the inevitable and rapid extinction of these cells, which at last have been forced to the production of a type lower in the scale than themselves. This process, therefore, soon negatives the remaining resisting power of the young columnar cell which is soon destroyed and thenceforward, direct cell multiplication by proliferation with consequent inevitable degeneration in type, proceeds from the newly produced polyhedral cells. The hitherto well marked basement membrane, upon which the columnar gland cells rest, is broken, and encroachment by the now potentially malignant cells proceeds beyond the normal confines. Moreover, the inflammatory exudate, hitherto mainly located outside the gland space, penetrates within the lumen and establishes direct contact with these cells, thereby increasing the rate of production and ensuring the onset of malignant change. The type of polyhedral cell produced from the columnar gland cell is seen to approximate rapidly to that produced by direct proliferation of squamous polyhedral cells. It is infantile in type and distended by deeply staining protoplasm. It possesses an ill defined and large nucleus and ill defined and large cell walls. A collection of these cells present the typical blurred appearance noted in connection with the cancer phase in squamous epithelium.

Whereas, however, the cancer phase is produced in squamous epithelium by the action of an irritant of the third degree of virulence in direct contact with otherwise normal if young polyhedral cells, it is necessary for an irritant of the first degree to penetrate the basement membrane of attenuated gland epithelium or, even if in direct contact with the cells from within the lumen, to stimulate this type of cell to its last response.

We have seen in the case of squamous epithelium that an irritant of the third degree stimulates without destroying—a necessity in the production of malignant change. An irritant of the first degree destroys the young polyhedral cells of the squamous layer. These are, however, very different in type from those produced by the young gland cell. They are normal cells in themselves, produced by the normal specific function of the basal layer, and for the purpose of a normal function when necessary (protective). On the onset of the cancer phase, we have seen that the density of the associated inflammatory exudate increases to that corresponding to the first degree, but cells potentially malignant or developed in malignancy are not now affected by this contact.

The cancer phase with regard to squamous epithelium, therefore, is developed from these young polyhedral cells, after destruction of the extremely attenuated basal layer. The cancer phase with regard to columnar gland epithelium is developed directly from the youngest proliferated cells—of similar morphology and function to that possessed by the highly resistant parent cells. The strongest irritant is, therefore, still necessary in its production. Cells, potentially malignant, are almost immediately produced, there being no true metaplasic function possessed by these gland cells, and the rapid and progressive degeneration in type proceeds in the presence of this irritant, which, in this case, is similarly inadequate to destroy cells that have definitely embarked upon the malignant course.

Figure 46 demonstrates the cell reactions which immediately precede the onset of malignant change in young columnar gland epithelium.

Here, one may observe a newly produced gland space, situated deeply. It owes its presence to proliferation from older gland elements in response to the presence of a surface ulcer. This gland space is surrounded by, and is in intimate contact with an inflammatory exudate of a density equal to an irritant of the first degree of virulence. The basement membrane is seen to be perforated from without and a quantity of inflammatory cells are observed to have penetrated, via this perforation, into the gland lumen. In another area the commencement of direct cell stimulation by polyhedral cell formation can be seen. This gland space is about to exert its final cell response prior to the inevitable onset of malignancy.

Figure 47 shows an adjacent gland space in the same section. Here the process has advanced to the definite degree of irregular

cell production and malignant degeneration. The gland space here shown is similarly surrounded by an inflammatory exudate of the first degree, much of which has penetrated into the lumen. Direct contact is made, both from without and within, with the gland cells. These are now seen to be transformed over the greater part of the circumference of the space, into a mass of ill defined but typical cells of the malignant type. The process here has only as yet just begun. The rapidly multiplying polyhedral cells are seen to conform still to the original outline of the epithelium from which they have sprung. The basement membrane has disappeared. New cells have encroached beyond the normal boundaries. A typical mass of blurred and deeply staining cells in intimate contact with a dense infiltration results. Part of this single gland space is as yet unaffected. The inflammatory infiltration in contact with this part is locally very slight. The columnar cells here have not been stimulated, hence they still remain normal. Here is yet another proof of the necessity of direct contact between exudate and cell to produce cell reaction.

In Figure 47 we see the earliest evidence of definite cancer in glandular epithelium. The two gland spaces shown in Figure 46 and Figure 47 are the only ones in the whole specimen which are affected in this way. Here again one sees the necessity for absolute contact between the inflammatory exudate cells and the epithelial elements before cell reaction takes place. Figure 47 demonstrates this fact well. Without contact there is no reaction.

Figure 48 demonstrates the relatively rare reaction of direct malignant gland proliferation, resulting in the production of a true adenocarcinoma. This reaction invariably takes place in association with the deeply placed and original gland elements and is provoked by their direct contact with a dense inflammatory exudate corresponding to an irritant of the first degree. My cases show that it is rare to find these old glands involved by direct contact with an irritant in the absence of a surface erosion. Even in the presence of this latter condition, the vast majority of cases show a relatively slight degree of direct involvement of the glands situated high in the cervical canal. The inflammatory exudate, in practically all the cases, is, for the most part, in association with the newly proliferated elements. An active irritant of the greatest virulence, involving the glands of the cervical canal locally, there being no spread to the portio or to the uterine cavity, is a very rare condition. A scrutiny of the cases of this series bears this out. I have said elsewhere that I believe these old glandular elements to be practically immune to cancer change. Their natural reaction to irritation is by direct proliferation. Very rarely is any other reaction required. Direct contact irritants are nearly always of a minor degree. The only irritant capable of calling forth an alternative reaction is one of the greatest virulence prolonged in its attack; that is, one acting directly upon these gland elements and analogous, either by reason of its own inherent virulence or by reason of the state of the patient's resistance, to that observed in the production of true surface ulceration. Under these conditions it is readily understandable that the natural and initial reaction of these gland elements to irritation will be provoked suddenly and continuously and out of proportion to their productive power, with the result that true glandular malignancy will be produced. I therefore regard these old gland elements as indestructible by pathological irritants.

The condition of solid alveolar carcinoma, resulting from the malignant production of polyhedral type cells from new columnar epithelium, as already described, is, however, the condition of importance, in so far as its occurrence is greatly in excess of true adenocarcinoma. We have completed our study of the incidence of the cancer phase in this respect. From this point it is but an insignificant step to that of developed cancer. My object in this instance therefore ends with the observation of this all important phase.

Developed cancer. I have only one thing to say with regard to developed cancer. It is necessary for me to emphasize my firm belief in the origin of carcinoma from pre-existing

epithelium. Wilson has pointed out the frequent histological demarcation which exists between the carcinomatous cells and those of the adjacent epithelium, and has suggested that the direct origin of the one from the other is not yet proved. More recently Schiller has noted this appearance and speaks of an "oblique groove" which runs between the benign and malignant tissues.

The cases of developed cancer in this series have also shown a distinct demarcation line in practically every case. I regard this, however, as an artefact, and produced in cutting the sections. The density of the normal epithelium and its subjacent tissues is much greater than the loose, semi-liquefied and almost entirely cellular malignant tissue which itself extends to a relatively great depth. There is a great difference in consistency between these two adjacent tissues. On cutting thin sections therefore it is almost impossible to prevent separation at their junction—especially at the surface.

Figure 49, however, shows a developed cancer and demonstrates the contact between the benign and malignant cells.

THE BASIC CAUSE OF CERVICAL CANCER

From the foregoing it will be seen that my endeavor, in attempting to elucidate the problem of the relationship between cervicitis (erosion of the cervix) and cervical cancer, and incidentally to acquire a knowledge of the nature of cancer inception, has been to place these conditions as a whole upon a common basis. A study of my cases has shown that the one phenomenon common to all is the associated presence of an inflammatory exudate. Also that epithelial reaction, no matter by what type of epithelium, depends entirely upon *intimate contact* between the cells of the exudate and the epithelium concerned. One has also learned that the type of epithelial reaction produced depends directly upon the nature and function of the epithelium, and also upon the density and accessibility of the inflammatory exudate in contact with it.

There has been no exception to these rules throughout this long series of cases. Epithelial activity has never occurred in the absence of a contact exudate. The type of reaction, under the various conditions, has been so constant as to impress me, beyond any doubt whatever, with the fact of the constancy of cell behavior. Once the relative values, in terms of age, function, and type, of these cells are understood, and the associated external factors taken into true account, one might almost evolve the histological picture which would result from any given combination. There is nothing atypical in cell behavior in response to irritation until malignancy is reached. Even then, the "anaplasic atypia" is merely a matter of the phenomenon of malignancy itself, and is in no wise concerned with the factors which produced it. Once the border line is crossed the causal agent plays no further part. The stimulus has been given. What proceeds thereafter does so, in spite even of many additional external factors which thenceforward are present, and is, in itself, progressive and inevitable. That, however, is not part of our concern. Our inquiry ends at the inception of this phase, which is brought about as the result of direct contact between inflammatory exudate cells and certain types of epithelial cells.

The inflammatory exudates observed throughout the whole of this series, and including those concerned in the production of the cell changes referred to, are typical and identical. There is no variation in type as far as the component cells are concerned. The relative numbers alone vary according to the degree of acuteness of the inflammation produced.

As previously explained, I have preferred to use the word "irritation" in preference to "infection" in dealing with these exudates, in so far as it is presumably possible for them to be produced by the action of purely chemical irritants as well as by bacterial organisms. The concentration of either of these agents, however, is in the immediate vicinity of the exudate produced, and there is no histological distinction in type resulting from their action, except, as I have said, in the matter of degree. These exudates, therefore, may result from the action of either of these agents. In the case of the cervix uteri, however, there

is no doubt that septic organisms (including the gonococcus) are very frequently concerned, and, in my opinion, it is impossible to ignore the fact that organisms of this kind are directly responsible in the production of most, if not all, of these exudates. The discovery of the exact organism or chemical does not concern us. There is no reason to disagree with Gye's theory of a filtrable virus in this respect. He has concentrated upon the recognition of the initial causal factor in the production of cancer.

The nature of cancer, when produced, also forms no part of this work. Blair Bell and others have probed deeply into that aspect. Blair Bell regards the initial causal factor as unimportant in comparison with the nature of cancer itself, from the point of view of treatment. It is toward the recognition of an *intermediate causal factor* that this work has been directed. Whatever the initial cause be, it is its direct expression which acts upon epithelial cells eventually to produce cancer change; and this—a typical inflammatory exudate—is a constant factor toward this phenomenon.

I have divided the exudates concerned into 5 types according to relative concentration (Part. 2, par. 1), thus representing irritants of five degrees of virulence. I have avoided a definite cell count in connection with this division on account of its arbitrary nature, as explained. Nevertheless I believe that in each individual case the actual cell concentration of this exudate marks the degree of irritation exerted by it upon epithelium in contact. The fact that exudates of equal density may be produced in different cases by organisms or chemical irritants of varying virulence according to the resistance of the patient concerned, is of importance, in so far as it increases the value—as the causal agent—of this intermediate factor, which alone acts constantly. The same initial factor, acting in a number of cases, might result in the production of exudates of varying density in each. The cell reactions would therefore also vary. Cancer may be produced in one and not in another.

The densities of the two chief exudates, those corresponding to irritants of the first and third degrees, are distinct. It has been seen that the action of an exudate corresponding to an irritant of the first degree of virulence is necessary to the production of cancer from columnar epithelium, and that one equal to an irritant of the third degree is sufficient in the case of squamous epithelium. In the latter case direct contact is assisted by subepithelial rarefaction. The exudate is in contact from below, but there has always been evidence of a surface gap from which direct subepithelial spread has undoubtedly been effected. I do not therefore consider this phase to be due to a secondary subepithelial irritation, emanating possibly from the blood stream.

I would, therefore, assert that the basic cause of cervical cancer is the effect of an inflammatory exudate (being the visible sign of an irritant of bacterial or chemical nature), acting directly upon epithelial cells, and of a density varying in accordance with the type of epithelium involved.

The nature of cancer inception is that of a pure cell reaction on the part of pre-existing but newly produced epithelial cells.

I do not believe that a single initial cause can produce this effect, constantly and in all cases, in connection with epithelium of one type alone, much less in connection with epithelia of different types. I do not therefore believe that there is one great initial cause concerned in cancer production, but that a variety of initial causes actually conduce to this end—through the agency of this single intermediate cause which alone is constant.

Cancer change in squamous epithelium is provoked by a re-irritation of new epithelium; in columnar epithelium, by a prolonged and constant irritation of great intensity, which is probably repeated many times.

As we have seen, the distinction between "new" and "old" squamous epithelium is arbitrary and not absolute. Epithelium of this type may be said to be "new" so long as the resistance of the columnar cells of the basal layer is less than the maximum resistance of the subjacent polyhedral cells. At the moment that the resistance of the basal layer becomes greater than that of the subjacent cells, in consequence of freedom from irritation or metaplasic activity over a period of

time, the epithelium concerned may be said to be "old."

In this respect, therefore, the phenomenon of cancer inception is a cell reaction which depends as much upon the time of its onset, within arbitrary time limits, as it does upon the factors which conduce to it.

CONCLUSION

Without further repetition, I have little to say in conclusion except that:

1. Cervicitis, erosion of the cervix, is definitely related to cancer of the cervix.

2. This relationship is effected through the agency of a factor common to both—an associated inflammatory exudate in contact with epithelium. This is the intermediate causal factor, and is constant.

3. The basic cause of cervical cancer is to be found in this constant factor which is associated with all cell reaction, including that of cancer inception.

4. The phenomenon of the action of contact inflammatory exudates of varying degree upon epithelia varying in type, forms this intermediate causal factor, or basic cause, in the production of cancer.

5. There is no one great initial cause of cervical cancer.

6. In the case of squamous epithelium the change is produced as the result of a re-irritation of minor intensity affecting newly produced cells. In the case of columnar epithelium it is produced by a prolonged and intense irritation affecting new epithelium—probably recurrent.

7. As far as the cervix uteri is concerned, I am inclined to the belief that the initial causal factor concerned in the production of the intermediate causal factor, is bacterial, and is moreover concerned to a large degree with the well known septic organisms. Recurrent attacks of specific intensity, from the epithelial standpoint, involving epithelium *during the danger period*, result in the production of cancer. The question of the time at which this attack is made, therefore, plays its part, and this fact is undoubtedly instrumental in minimizing this catastrophe.

Whatever initial causes there are in the production of cancer growths, whether bacterial or chemical, the effect is produced through the agency of this constant intermediate factor. The result is the production of the cancer process, which again may be variable in its intrinsic nature, although in relation to the epithelia of the cervix uteri this phenomenon shows a rare degree of consistency.

I wish to emphasize, therefore, that whereas there may be, and in my opinion undoubtedly are, many initial causes in the production of cancer, and the nature of the growth itself may even be atypical, nevertheless there is always one factor concerned in this process which remains constant in type for all epithelia, and, moreover, constant in degree according to the nature of the epithelium concerned. It is this, therefore, the intermediate causal factor which I have described, which in my opinion is of such great importance in association with the phenomenon of cancer inception.

As I have said elsewhere, the nature of cancer inception is that of a pure cell reaction, dependent alike upon the type of epithelium involved, the span of time during which the young cells are affected, and the degree of intermediate causal association with them at that time.

8. Alterations in the densities of contact inflammatory exudates results in alterations in the cell reactions produced, *ipso facto*. An alteration in the density of the exudate concerned during the epithelial danger period, whether pathological or therapeutic, would result in an altered cell reaction. Involved epithelium at this stage must frequently just escape cancer change through pathological means, resulting from coincident changes in inherent resistance. Is it possible to effect the same result by therapeutic means?

SPASTIC ILEUS

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IN the final decade of the last century the idea became current that spasmodic contraction of the intestinal musculature might obliterate the lumen of the bowel for a varying period of time and lead to the picture of intestinal obstruction. Israel speculated on the phenomenon of obturating gall stones which became fixed after having traversed a portion of the intestinal tract without difficulty, and he attributed part of the occlusion to contraction of the bowel wall about the concretion. Koerte, too, was impressed by the fact that small stones not infrequently gave rise to intestinal obstruction. He hypothesized that the stone delayed the passage of intestinal contents without actually obstructing them. Fermentation then occurring in the stagnant contents released irritating substances which provoked exaggerated peristalsis and spastic contraction of the bowel about the stone. It remained for John B. Murphy, however, to demonstrate a spastic occlusion of the intestine at laparotomy in a patient suffering from lead poisoning. In 1897, the year following, Haidenhain, in a paper read before the German Surgical Society, presented spastic ileus as a clinical entity and reported 3 cases in which the enterospasm was demonstrated at operation. There was considerable opposition to the statements of Haidenhain at that time but, in the 30 years that have followed, the existence of a spastic or dynamic form of ileus has become established beyond reasonable doubt. The total number of reported cases, however, is not large. Fromme, in 1914, collected 20 cases in which the diagnosis was confirmed at operation. In 1920 the number, according to Sohn, had reached only 30. The following year Nagel gathered from the literature 51 cases which had been proved at operation or autopsy. I have collected 157 cases from the literature, in which the condition has been adequately demonstrated on either the operating or postmortem table, or both, and to this number have added two observations of my own. The reported cases probably constitute only a small percentage of the total number occurring, as is evidenced by the fact that Koerte was able to report 28 of his own cases, all of which were confirmed at operation or autopsy. It is highly probable that many of the cases of intestinal obstruction which have responded to treatment with antispasmodics, heat, or other non-operative measures were really spastic in origin.

Spastic ileus has been defined as an intestinal obstruction the origin of which depends solely on a persisting contraction of the intestinal musculature. According to an excellent description by Freeman, "Spastic ileus is due to a spasmodic muscular contraction of a portion of the intestinal tract. It may affect either the small or the large bowel or both; in one place usually, or possibly in many places. It generally includes a few inches of the gut only, although at times a considerable length is compromised. A common location is the lower portion of the ileum. The typical appearance is striking and unmistakable. A section of gut a few inches in length is contracted to the limit, rendering it white, bloodless, and so firm that it often may be picked up by one end and held horizontally without bending. The contracted part does not merge gradually into the adjacent bowel, but stops abruptly at either end, the rest of the intestine remaining normal; but if the trouble lasts long enough the proximal bowel dilates, as in any other form of obstruction. The spasm frequently persists after the abdomen is opened, although it may disappear, and it is sometimes found even at autopsy." It might be added that often the manipulation incident to laparotomy and exploration is sufficient to cause the spastic portion of bowel to relax, and the collapsed segment has frequently been observed to fill out under the hand of the surgeon.

Because its clinical picture lacks exact definition, spastic ileus does not lend itself well to statistical study. It is difficult to establish

a positive pre-operative diagnosis and often impossible to rule out mechanical factors. It has, therefore, been correctly stipulated that only those cases in which the diagnosis has been verified at operation or autopsy should be tabulated. Many cases which occur and subside spontaneously or with conservative treatment would be omitted in such a study. Nor will the operative or postmortem findings include all cases. Although the spasm often persists in spite of general anæsthesia, it is probable that it sometimes yields in narcosis; and though spastically contracted bowel has been found at necropsy, it is to be assumed that in some instances the contractions will have relaxed in death. On the other hand, it is possible that spasms found at autopsy may have been agonal rather than factors in the cause of death. Furthermore, there is no sharp limitation as to what shall be included under the term spastic ileus. The clinical picture of enterospasm varies from the acute, severe cases, which simulate acute mechanical obstructions, through the subacute and chronic forms, to the mild spasms which cause simple constipation or slight discomfort suggestive of gall-bladder or appendiceal disease. Again, if spasm plays a part in obturating obstructions, as Israel and Koerte have suggested, which cases shall be ascribed to the foreign body and which to the spasm? Finally, it has been claimed that intussusception often begins as a spasm, and localized spastic contractions have been seen accompanying or following the reduction of invaginations. A sharp differentiation between these two conditions is, therefore, often very difficult.

Spastic ileus, like other functional disorders, may result from a wide variety of different conditions, and considerable discussion has arisen as to the mechanism of the contraction. Frequently, several factors seem to be present, and various writers differ as to the relative importance of the individual components. There are those who see local irritation of the bowel or of its adjacent structures as the dominant cause. Some ascribe the greatest importance to changes in the vagus nerve or the retroperitoneal plexus, and others lay the condition essentially to psychic disturbances. Pototschnig assumes the presence of a "tendency to spasm" of the autonomic system as a necessary prerequisite of spastic ileus. Steindl has found organic changes in the medulla of patients dying of spastic obstructions and believes that such occurrences are due primarily to a pathological condition of the central nervous system. Payr, on the other hand, has succeeded in demonstrating spasm of the intestinal musculature from experimental occlusion of the mesenteric vessels and would explain the phenomenon on a circulatory rather than on a nervous basis, at least in the traumatic forms. Obviously, no one explanation is adequate to account for all of the observed cases.

The innervation of the bowel is very complicated and not entirely understood. According to Mueller, it seems that most of the motility is controlled by the intrinsic nervous plexus, the plexus of Auerbach and Meissner. In addition the function of the bowel is under control of the vagus and sympathetic systems by way of the cœliac and inferior mesenteric plexus. And over all, exerting some measure of control, is the central nervous system. From the great diversity of causes of spastic ileus described, it would seem that stimuli arising in any portion of this nervous apparatus may produce the spasm that interferes with the passage of intestinal contents. The causes of spastic ileus, therefore, fall into three groups, corresponding to the three major divisions of the nerve supply to the bowel.

SPASTIC ILEUS FROM STIMULI ACTING ON THE BOWEL AT THE SITE OF SPASM

Every surgeon has seen transient spasms of the intestine from pinching or squeezing during the course of abdominal operations, and contractions of longer duration have been produced experimentally by the use of stronger stimuli. Thus mechanical, thermal, or electrical irritation, the injection of physostigmin into the lumen, or the painting of adrenalin or barium chloride solution on the serosa have all been found to give rise to such spasms. Moreover, excised portions of bowel (Magnus) will respond in the same way to these stimuli, indicating that the reflex is an intrinsic one, by way of the Auerbach and Meissner plexus. Clinically, cases of spastic ileus have fre-

quently been reported due to local irritants analogous to the experimental ones mentioned.

Foreign bodies. Israel and Koerte, as stated before, both described intestinal obstruction from small gall stones which had traversed part of the intestinal tract without difficulty, and they ascribed the occlusion to spastic contraction of the bowel about a stone. Similar spastic segments, due to scybala, have been seen by Schloffer and Sohn, Vogel has reported a case of spastic ileus due to fruit seeds which produced a picture as threatening as one of mechanical obstruction. The foreign body was pushed into the cæcum at laparotomy, and the patient recovered. There is probably an element of spasm in most cases of obturating obstruction. It is difficult to explain why such objects as fæcaliths, gall stones, or fruit seeds, which so frequently form part of the intestinal content with no untoward effect, should, in the exceptional case, lead to severe enough irritation to cause spastic occlusion of the bowel. Perhaps the assumption of Koerte that irritating substances develop in the stagnating contents behind the obturating body will account for it, or it may be, as Florack suggests, that decubitus ulceration from the pressure of the foreign body gives rise to the spastic reflex.

Intestinal worms. An interesting group of cases due to the presence of foreign bodies is the one caused by intestinal parasites. Two types of intestinal obstruction due to worms have been described: an obturating ileus from massed clumps of parasites and a spastic ileus about one or several worms. Even in the former group, an element of spasm may play a part in the final obstruction. Cases of the second type have been reported by Haidenhain, Hagedorn, Kiesselbach, Kuester, Rost, and Schulhof, in which the spasm was due to ascaria; Barth's case was due to tapeworm; and Dmitrieff's case resulted from oxyuria. Rost observed in 1 year 4 cases in which operation was performed, and he attempted to determine experimentally the cause of the spasm. In testing the effects of extracts of various portions of round worms on the musculature of excised intestine of the cat, he found that extracts of the digestive and genital organs increased the tonus while that of the skin depressed. He, therefore, concluded that living worms could produce intestinal obstruction by forming large obturating masses, and that spasm was due to death and disintegration of the parasite. Sohn, however, maintains that the irritation is a mechanical one, and his view is supported by the instructive observation of Kuester, who found enterospasm due to a worm at laparotomy and could make the spasm travel up and down as the parasite was pushed to and fro in the intestine. In the case due to oxyuria (Dmitrieff), an ulcer had been produced by the worm, which had perforated to the serosa. It is possible that some of the cases in which no cause for the spasm could be found at operation may have been due to intestinal parasites. Nordmann operated upon a child 2 years old under the diagnosis of strangulation ileus and found spasm. No cause was discovered, and only after the child passed a clump of worms a year or so later was the etiology of the attack explained. Barth's patient developed spastic ileus following colporrhaphy. At laparotomy enterospasm was found without attributable cause, and only autopsy revealed the tapeworm in the contracted portion of the bowel.

Undigested food. Several cases are on record in which no other cause for the enterospasm could be found than indigestible foodstuffs. Engstad recently reported one in which the patient gave a history of having eaten at least twelve ears of sweet corn on the preceding day, and another in which excessive intake of ice water on a very hot day seemed to be the sole cause of the attack. The latter case has its counterpart in the "heat cramps" frequently observed in industry, which rarely come to operation and which are not, as a rule, thought of as potential spastic obstructions. Kelly and Pototschnig have each reported a fatal case of spastic ileus, in which no other factor than undigested food or excessive intake could be found at operation or autopsy. Intestinal spasms and intussusceptions in infants may well be on the basis of the ingestion of irritating foods.

Bleeding into the intestine. The escape of blood into the gastro-intestinal tract often

acts as an irritant, as is witnessed by the frequent vomiting and diarrhœa following massive gastro-intestinal hæmorrhages. Jenckel describes spastic ileus following resection of a carcinoma of the colon. Laparotomy revealed massive hæmorrhage from an overlooked duodenal ulcer, with extreme contraction of the entire small intestine. Franke reports two similar cases, one of which was likewise demonstrated at operation.

Ulceration. As mentioned before, decubitus ulceration may be the immediate cause of enterospasm in the presence of foreign bodies or intestinal worms, just as ulcers elsewhere in the alimentary tract often give rise to spasms at their sites. Strehl has had a case of ileo-cæcal tuberculosis with increasing obstruction. At operation, fifteen segments of spastically contracted bowel were seen, corresponding to which were the multiple tuberculous ulcers found at autopsy.

Hernias. One of the most frequently observed local causes of spastic ileus is strangulation in a hernial sac. The spasm persists after spontaneous or operative relief and is due, apparently, to damage to the bowel during the period of strangulation. Brunzel has observed 3 such cases, 1 of which followed strangulation of an umbilical hernia. Similar observations are reported by Barth, Brunn, Melchior, Florack, Reiss, and Kessler. Wilms has called attention to the fact that strangulation of a Littré hernia also may be followed by spastic occlusion of the bowel. This group of cases suggests that some of the mishaps following taxis or reduction of strangulated hernia may have been due to persisting spasm at the site of strangulation.

Circulatory disturbances. Payr has shown that the injection of solid particles into the mesenteric vessels, producing artificial emboli and local anæmia, causes maximal contraction of the affected portion of bowel, and he has reported a case of spastic ileus due to torsion of the omentum with thrombosis of the veins. Mueller states that arteriosclerosis of the mesenteric vessels may give rise to enterospasm, and Lecène reports one such case in which no cause other than sclerosis of the vessels supplying the spastic segment of the bowel could be found. Some of the cases following operation or intestinal strangulation may have their origin in disturbances in the blood supply of the affected portions of the intestine.

REFLEX SPASTIC ILEUS DUE TO DISTANT LESIONS

The occurrence of spastic ileus from intrinsic reflexes as described above is readily understood. Less clear are those cases which seem to arise from irritants acting at a distance, the effect of which must be by way of an extrinsic reflex. While it is true that most of the control of the motility of the bowel is effected by the myenteric plexus of Auerbach and Meissner, the cœliac and inferior mesenteric plexus, made up of sympathetic and vagus elements, do exert some control. Talma demonstrated experimentally that vigorous stimulation of the cœliac ganglion resulted in active motility of the intestine, chiefly in the form of spasmodic contractions. There are on record several clinical cases of spastic ileus, which were due to inflammatory or cicatricial processes involving the cœliac plexus. Maier and Mosse have demonstrated changes in the cœliac ganglion in experimental lead poisoning, to which they attribute the colics and spasms accompanying this condition. Recent observations with regional and spinal anæsthesia have given further support to the assumption that irritants at a distance, acting by way of the extrinsic reflexes, may cause spastic ileus. Denk states that, with satisfactory injection of the splanchnic plexus (by the Kappis method), he often notices moderate cyanosis and definite spasms of the bowel. Wagner found that spinal anæsthesia was frequently sufficient to initiate peristalsis in paralytic ileus, and his observations have been confirmed experimentally and clinically by Markowitz and Campbell, and Ochsner, Gage, and Cutting. Mayer made similar observations and noted further that spastic ileus could also be relieved by intraspinal anæsthesia. French surgeons, in particular, have adopted spinal anæsthesia as a treatment for ileus, and Duval has collected 400 cases in which it has been used. Of this number 8 were said to have been cases of spastic ileus, and in every instance the condition was defi-

nitely relieved by the spinal injection. The relief of obstructions due to atony and spasm by the same measure would appear scarcely credible, but Colmers explains the apparent contradiction as follows: Normal tonus of the intestine depends upon a balance between the pressor effect of the vagus and the depressor influences of the splanchnics. Should the balance be disturbed by excessive stimuli from either of these systems, interruption of the abnormal impulses by spinal anæsthesia would promptly restore the normal status. Granting that the action of stimuli by way of the vegetative nervous system may lead to the picture of spastic ileus, it will be seen that these stimuli may be direct, acting on the nerves or ganglion cells themselves, or indirect, acting by way of reflex irritation.

Lesions involving the cœliac plexus. Exner and Jaeger report a case of spastic ileus due to an inflammatory lesion of the posterior wall of the pylorus, with involvement of the retroperitoneal nerve plexus. Klett's case was due to carcinoma of the pancreas with retroperitoneal extension, and Prader's to acute pancreatitis. Koennecke saw two such patients, one with an inflammatory tumor of the pancreas and one with an ulcer which penetrated into the pancreas. Although changes in the cœliac ganglion have been described in experimental lead poisoning, the evidence has been held inadequate to warrant placing the cases of spastic ileus due to plumbism in this group.

Spastic ileus following contusions to the abdomen. While spastic ileus occurring after blunt contusions to the abdomen may be the result of injury to the bowel itself, it more often appears to be reflex from trauma to peritoneal surfaces. Several cases of this type are on record. Rehn operated upon a patient 9 hours after a severe contusion, with diagnosis of ruptured bowel. A portion of the sigmoid, corresponding in position to the site of the traumatism, was found contracted down to the diameter of a finger. Beyond this there was nothing, and recovery followed the simple laparotomy. Trendelenburg has opened the abdomen twice, following contusions, to find localized spasm of the bowel. Often the injury which gives rise to the spasm is not severe. Fromme reports a case in a child, aged 11½ years, who was running on a springy wooden floor, and another in which the patient fell and fractured several ribs. I have seen a case very similar in its etiology to this last one.

CASE 1. The patient, J. H., a male aged 27 years, fell from a scaffold about 25 feet high, while at work on the morning of December 10, 1927. He was admitted to Wesley Hospital about an hour later, in a state of moderate shock (blood pressure, 90–60) and complaining of pain in the back. The X-ray picture revealed an oblique fracture of the right transverse process of the first lumbar vertebra, all other bony structures being normal. The temperature was subnormal, and the pulse rate was 80. The abdomen was diffusely and uniformly rigid but was neither tender nor painful, and there were no external evidences of injury to the abdomen. No neurological findings were elicited. During the ensuing 24 hours the patient recovered from his shock and the abdominal rigidity relaxed somewhat. About 28 hours after admittance he began to complain of severe, intermittent, cramp-like pain referred to the region of the umbilicus, which soon became so acute as to cause him to cry out with each paroxysm. Vomiting occurred twice. The pulse rate rose rapidly to 122, and the abdomen became slightly distended, but the temperature remained normal. Some of the rigidity was still present, and there was very slight tenderness in the right lower quadrant. Peristaltic sounds were increased, and vigorous peristaltic waves were heard to accompany the paroxysms of pain. Because of the picture of mechanical ileus, the abdomen was opened under nitrous oxide anæsthesia. Exploration of the entire abdominal cavity revealed no evidence whatsoever of trauma. A segment of ileum about 3 feet long was found to be collapsed, empty, and ribbon-like. At either end the collapsed portion merged with normally distended bowel. There was no obstruction or other abnormality at these points. During the manipulation incident to the examination, the contracted segment was seen to relax and resume the appearance and caliber of the rest of the bowel. The abdomen was closed without drainage. On the following day the patient had several paroxysms of abdominal pain which responded readily to opiates, atropin, and external heat. Convalescence was rapid, and there were no other symptoms attributable to his injury or operation.

Reimer lays great stress upon the irritating action of extravasated blood in the peritoneal cavity on the production of spastic ileus. He cites 3 cases following abdominal contusions, 2 of which were operated upon, in which the spasms persisted until the hæmoperitoneum was evacuated. A series of patients with

ruptured extra-uterine pregnancies were closely questioned, and it was thought that a history could be elicited in every instance of pain, suggestive of intestinal spasm, following the severe, tearing pain of the rupturing tube. In support of this may be mentioned the experience of Jordan, who operated for ruptured spleen following trauma and found in addition spastic contraction of the sigmoid and half of the small intestine.

Postoperative spastic ileus. While most functional disturbances of the bowel following operations are paralytic in nature, occasionally true spastic obstructions are encountered. It is difficult to state whether these are due to trauma of the bowel during the laparotomy or to thrombosis of the mesenteric vessels, or whether, in certain cases, they may not be due to beginning peritonitis or even to the primary condition for which the operation was performed. It is hard to understand why trauma, which usually gives rise to intestinal paresis or paralysis, in these cases produces the opposite reaction. Furthermore, it has often been noted that the manipulation during re-operation has brought about relaxation of the spasm induced by the original operation. Braun and Wortmann state that intestinal spasm and intestinal paralysis may be caused by the same factors, that both may be present simultaneously, and that intestinal paresis may be preceded by a state of spasm. Spastic ileus following operation has been seen with particular frequency after gastric and gynecological procedures. Koerte has observed 6 such cases, 5 of which ensued after gastro-enterostomy. I have also seen a case following operation for peptic ulcer.

CASE 2. The patient, A. S., a male aged 46 years, was operated upon for perforating post-pyloric ulcer. Resection and retrocolic side-to-end gastrojejunostomy (Pólya) was done. Mobilization of the duodenum was very difficult because of the extensive inflammatory adhesions, and considerable soiling occurred, requiring the placing of a drain down to the duodenal stump. On the second day symptoms of obstruction appeared, which were thought to be due to mechanical block at the site of anastomosis. Re-operation revealed local peritonitis about the stump of the duodenum. The gastrojejunal stoma was free and intact. The stomach and proximal half of the small bowel were dilated; the distal half was empty, collapsed, and contracted. The point of transition between the distended and collapsed portions was abrupt and free from any abnormality whatsoever. Jejunostomy was done and the abdomen closed. Death occurred 3 days later, and autopsy revealed localized peritonitis as its cause. No statement was made as to the condition of the small bowel at that time.

It is significant that in the cases observed by Koerte, in which spastic ileus followed gastro-enterostomy, several times the spasm was located in the jejunum. We know from the experimental ulcer studies of Mann and his co-workers that the acid contents of the stomach are irritating to the jejunal mucosa. This suggests the possibility that these cases arise frequently after gastric operations because of the local irritating action of the stomach contents on the jejunum, which produces local spasm. This also may explain certain cases of "vicious circle" following gastrojejunal anastomoses, particularly those in which re-operation fails to reveal a mechanical explanation for the accident. The following case may have been illustrative of this occurrence.

CASE 3. The patient, M. F., a male 56 years old, was operated upon for very early carcinoma of the stomach. Partial resection was done, with retrocolic end-to-side gastrojejunal anastomosis (Pólya), and an uneventful recovery ensued. The patient, however, complained of fullness, as though of gas, in the epigastrium and chest, with relief on eructation. X-ray examination 12 days after the operation showed a large fundal portion remaining with a 5 hour residue. Patient left the hospital on the following day, but was compelled to return a week later because of persistent vomiting. Aspiration revealed high grade retention, and re-operation was done. No obstruction could be found. The line of anastomosis was completely freed and found entirely satisfactory. Incision was made into the stomach above the anastomosis, and a good free opening into both jejunal loops could be demonstrated. The opening was enlarged somewhat, and the gastrotomy incision closed. An entero-anastomosis was done just below the gastrojejunal stoma, and the jejunum was sutured to the colon to insure against invagination. The patient made a slow recovery, since convalescence was delayed by the development of a fæcal fistula.

In a rather extensive series of currently appearing articles Reischauer has voiced a similar opinion regarding the relation of vicious circle to enterospasm, and he has attempted to show, moreover, that most of the

other obstructions following stomach operations have their origin in spasm.

Spastic ileus accompanying lesions of other organs. Those cases of spastic ileus associated with lesions of other intraperitoneal, or even with extra-abdominal, structures would seem of necessity to be reflex in origin. One interesting group of this type is that due to mechanical obstruction involving some other bowel segment. Thus Haidenhain, Jenckel, Schlesinger, and Brunn have seen spasms of the small bowel associated with carcinoma of the rectum; Miller's case was associated with mechanical obstruction of another loop of bowel by a band; Barsony's patient had tuberculosis of the cæcum producing spasm in the ileum; and Haidenhain's patient had volvulus. Whether the spasm in these cases is reflex or whether it is due to stagnation of contents above the mechanical obstruction cannot be determined. Franke saw enterospasm during operation for peptic ulcer, Braun and Wortmann saw enterospasm from hydrocele, Mueller from early appendicitis, Brodnitz from adrenal hæmorrhage, Engstad from cystic ovary, and Huguier and Parvu from renal colic.

A word should be said regarding the relationship between intestinal spasm and intussusception. Nothnagel demonstrated experimentally that invagination could be produced by causing local spasm of the bowel by means of faradic stimulation. He believed that clinical intussesception began as enterospasm. This theory has been substantiated by the experiments of Propping and others and by numerous clinical observations. Fromme describes a case in which symptoms persisted after release of an invagination and resulted in the death of the child patient. At autopsy spastic narrowing of the small bowel was seen. In 2 other cases observed by the same author intussusceptions and enterospasms were seen simultaneously, apparently having had a common origin. It would seem, therefore, that enterospasm and invagination may arise from the same source and may be present simultaneously. Localized spasm may lead to intussusception, and injury to the bowel during intussusception may determine an enterospasm which may persist after release of the invagination and may even result in the death of the patient.

CAUSES ACTING BY WAY OF THE CENTRAL NERVOUS SYSTEM

Although there is no known "center" for intestinal control in the brain, nevertheless some degree of influence is exerted on the bowel by the central nervous system. This finds expression in the frequently observed emotional diarrhœas, which, like the vomiting that often accompanies intense psychic stimulation, denote a connection between the cortical centers and the gastro-intestinal tract. Spastic ileus has been described accompanying both organic lesions and psychic disturbances. Steindl, as mentioned, found degenerative changes in the medulla of 2 patients who died of postoperative spastic ileus. He believes that there must be a "tendency to spasm" as a prerequisite to the development of enterospasm and attributes the increased irritability to organic changes in the brain stem. So bold an assertion requires wide confirmation beyond the few instances he has described. Schuele has seen enterospasm for which no local cause could be found, and only autopsy several months later revealed a small inflammatory tumor in the floor of the fourth ventricle as a source of the mischief. Spastic ileus has been seen, too, in tabes dorsalis, and Deutschlander states that enterospasm frequently occurs in Little's disease. The cases due to lead poisoning might be placed in this group, as might also those observed in influenzal infections.

Much has been written regarding the rôle of hysteria in the etiology of spastic ileus. Some of the earlier writers have even gone so far as to state that a hysterical background is necessary to the development of such a condition. It would seem that the term hysteria has been rather loosely used in this connection. There are cases, described as hysterical ileus, in which the picture of intestinal obstruction was fictitiously assumed by the patient, even to the swallowing of fæcal matter in order that it might later be vomited. These, obviously, have nothing in common with spastic intestinal occlusion. There are other instances in which a history

and stigmata of hysteria are present, but in which there is also some local cause for the enterospasm. Finally, there is the group in which no regional explanation is found, and in which "hysteria" has often been invoked to account for the occurrence. In some of these last mentioned cases, local causes may well have been present though undiscovered. In others, simply increased local or general irritability of the nervous system may have determined the spasm. In none does the term "hysterical" seem justified. We recognize different degrees of irritability in the nervous systems of different persons, and it is to be expected that the most sensitive nervous apparatus is most likely to give exaggerated responses to ordinary stimuli. In its final analysis the matter reduces itself to the relative intensity of the stimulus for the irritability of the affected nervous mechanism.

To sum up, enterospasm is a state of exaggerated contraction of a portion of the intestinal musculature, which leads to obliteration of its lumen and owes its origin to a stimulus that is excessive for the degree of irritability of that particular nervous apparatus. The stimulus giving rise to the spasm may act anywhere in the complicated nervous system supplying the bowel. In some cases the irritability of the local or general nervous mechanism may be so greatly increased that spasms will occur without known extrinsic cause.

ANALYSIS OF THE COLLECTED CASES

I have collected from the literature 157 cases of spastic ileus (Table I), in which the findings at operation or autopsy were sufficiently definite to warrant their acceptance, and to this number have added the 2 cases here reported. Of the total 159 cases, 56 occurred in males and 73 in females. In the remaining 30, the sex was not stated. The ages varied from 5 months to 82 years. Three of the patients were infants less than 1 year old and 17 were children under the age of 15 years. The largest number, however, were adults in the middle span of life, 78 of the 129 stated ages falling between 20 and 60. The cause of the enterospasm was either not determined or not stated in 39 cases. In another 39 cases the contraction occurred seemingly in response to local or intrinsic causes; in 57 cases the contractions appeared to be reflex; and in the remaining 24 cases they were due to disturbances of the central nervous system.

CLINICAL PICTURE

The clinical picture of spastic ileus is the clinical picture of mechanical ileus. Like mechanical obstructions, the spastic occlusion may be acute or chronic, may be high in the small bowel or in the colon, and may be incomplete with mild manifestations or complete with the full stormy picture of bowel obstruction. The phenomena dependent upon strangulation, however, are absent. Only one difference in the manifestations of spastic and organic occlusions has been encountered with any degree of consistency: the general condition of patients having functional obstructions is good as compared with that of patients having mechanical ileus. Furthermore, spastic obstructions are much more apt to be intermittent and to subside spontaneously. It must not be inferred from this, however, that a differentiation on this basis is clinically possible. Cases of enterospasm are reported in which the patients presented the picture of serious collapse, and death has not infrequently occurred from purely spastic occlusions.

The onset of symptoms may be gradual or abrupt. The patients usually complain of severe, cramp-like pain, vomiting, and obstipation. Tympanites may or may not be present. If the case is seen early, no dilatation of the proximal bowel is found; if seen late, the abdomen may be ballooned as in neglected mechanical obstructions. Similarly, if the spasm is high in the alimentary tract, there will be no distention; if it is low, abdominal distention may occur. Furthermore, if the major portion of the bowel is involved and is spastic and contracted, the abdomen may be scaphoid rather than distended.

Haidenhain called attention to a bradycardia in his cases, and several subsequent authors have observed a similar symptom. This has been attributed to vagal irritation and has been considered by some to be of diag-

nostic value. It is very inconstant, however, for many cases with a marked tachycardia, rather than with a slowing of the pulse rate, have been described. In the cases which I have reported there was no noticeable slowing of the heart rate. In the first the pulse rate rose rapidly as the symptoms of ileus developed. In the second case definite tachycardia prevailed.

The diagnosis of spastic ileus cannot be made before the abdomen is opened. There are no criteria by which a given case of ileus may be definitely adjudged spasmodic, and attempts to do so which lead to delay in operation should be avoided. At laparotomy the diagnosis of spastic ileus is permissible when spasm of the bowel is demonstrated and when there is no mechanical cause for the obstruction.

The findings at operation vary considerably, but, in general, three types of contractions have been found. The most frequent condition is a spasm of one or more segments of considerable length, varying from a few inches to a number of feet. In some instances the entire small bowel has been compromised. The affected portion is usually described as being empty, pale or mottled in color, of increased consistency, and resembling tape or ribbon or having the caliber of a pencil, of rope, or of a finger. The second type of contraction is a ring-like furrow, "as if a string had been tied around the gut." In a few instances multiple, transient spasms, moving from place to place along the course of the bowel, have been encountered.

The prognosis of spastic ileus, in the uncomplicated case, is said to be good. Nevertheless, death has not infrequently resulted. In the 159 collected cases, 102 patients recovered, 47 died, and the outcome in the remaining 10 was not stated. This constitutes a mortality rate of 31.6 per cent in those cases in which the outcome is given. Of this number, however, 9 (6.2 per cent) presented spastic ileus as a more or less incidental finding and not directly as a factor in the cause of death. Thus, in 2 cases death resulted from uræmia and in 1 case each from meningitis, encephalitis, brain tumor, retroperitoneal phlegmon due to carcinoma of the rectum, pulmonary embolism following rib fracture, pneumonia after operation for intussusception, and ileocolostomy for intestinal tuberculosis. In 19 additional patients (12.8 per cent) it was a contributory factor but not the sole cause of death. Many of the postoperative cases fall into this group. In the remaining 20 lethal cases no other cause of death was found, and in these the fatality must be attributed directly to the enterospasm. Of the patients who did not succumb to the disease, there were some who were not cured. Although the subsequent history of most of these persons is not stated, in 14 (14 per cent) symptoms recurred after operation. Some of this group responded to medical treatment, others submitted to repeated operations, and in several the condition apparently persisted indefinitely, in spite of all treatment. From this review, it is seen that spastic ileus, while apparently offering a good prognosis in uncomplicated cases, has been associated with a very considerable mortality and persistent morbidity in the entire series.

The treatment of spastic ileus is essentially surgical. If it were possible to make a positive pre-operative diagnosis of enterospasm, temporizing with conservative measures, such as the use of morphine, atropine, and external heat, would be justified. Inasmuch as the diagnosis cannot be made with certainty, however, every bowel obstruction must be considered

TABLE I.—ETIOLOGY AND MORTALITY IN ONE HUNDRED AND FIFTY-NINE CASES CONFIRMED BY OPERATION OR AUTOPSY

Cause of enterospasm	Recovered	Deaths	Not stated	Total
Local causes:				
Foreign bodies	3	3		6
Intestinal worms	12	2	1	15
Irritating foods	3	2		5
Bleeding into bowel		1		1
Strangulated hernias	7	3		10
Ulceration	1	1		1
Circulatory disturbances		1		1
Reflex causes (by way of cœliac and inferior mesenteric plexus):				
Lesions involving cœliac plexus	0	4		4
Contusions of abdomen and adjacent areas	9	1		10
Postoperative spastic ileus	12	11	1	24
Lesions of other organs	11	5	2	18
Intussusception		1		1
Causes acting by way of central nervous system:				
"Hysteria"	10	1		11
Grippe	4	2		6
Uræmia	2	2		4
Lead poisoning	2			2
Brain tumor	1			1
Cause not determined or not stated	26	7	6	39
Totals	102	47	10	159

organic in nature until proven otherwise. Surgery must, therefore, remain the treatment of choice. What is done when the abdomen has been opened will depend somewhat on the cause of the spasm and the condition of the patient. As has been stated, usually the manipulation incident to the laparotomy has sufficed to bring about relaxation of the contraction. If the cause of the ileus can be corrected at the same time, this should, of course, be done. In the occasional case, in which the condition of the patient is seriously impaired by long standing obstruction, enterostomy may be advisable. Amberger strongly urges enterostomy in every case of spastic ileus, feeling that one of his patients might have been saved had this been done. In those instances in which the spasm is not due to purely local factors, there is no assurance that it will not recur in other places after enterostomy at the site of the original contraction has been done. Resection or entero-anastomosis hardly seem indicated for obstructions of spastic origin. After the diagnosis has been definitely established at operation, further postoperative treatment with sedatives, antispasmodics, and external heat should be carried out. It must be remembered that operation for the relief of a spastic bowel occlusion may in turn give rise to a mechanical obstruction which can be alleviated only by a second operation.

SUMMARY

Spastic ileus is a form of intestinal obstruction the origin of which depends upon a persisting contracture of the musculature of the bowel, leading to obliteration of its lumen. The spasm producing the occlusion is usually of nervous origin and is due to a stimulus which is excessive for the degree of irritability of the local or general nervous apparatus involved. The impulse may arise in any portion of the complex nervous mechanism controlling the motor function of the bowel. The cases, therefore, fall into three groups corresponding to the three major divisions of the nerve supply to the intestinal tract. Thus, we see spasms from irritants acting locally, at the site of spasm, by way of the intrinsic nervous plexus; reflex spasms, through the cœliac and inferior mesenteric plexus, from lesions distant from the spastic bowel segment; and those enterospasms arising from organic or functional disturbances of the central nervous system. If the local or general nervous irritability is sufficiently increased, excessive contraction may result from physiological stimuli, and no extrinsic cause for the spasm may be found. The clinical picture in spastic ileus is the same as that in mechanical obstructions, except that intermittency and spontaneous recovery are more apt to occur, and the general condition of the patient is usually less seriously impaired. The diagnosis cannot be definitely made except at operation, and is then acceptable only when the spasm is demonstrated and no organic obstruction is found. Treatment is essentially surgical, most cases responding to simple laparotomy. The prognosis is said to be good in uncomplicated cases, although, in the series of 159 cases analyzed, there has been a considerable mortality and a number of the patients have continued to have symptoms in spite of all types of treatment.

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CLINICAL SURGERY

FROM ST. STEPHEN'S HOSPITAL, BUDAPEST

OPERATION FOR CARCINOMA OF THE SIGMOID[1]

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DANGERS AND COMPLICATIONS

INSECURITY of the suture line is the principal danger in operations upon the sigmoid and other portions of the large bowel. Suture of the large intestine is much more difficult than that of the small intestine because of its wide mesenteric attachment and its fatty appendages. In addition, the large intestine is thinner and has a poorer blood supply. The presence of dry, hard fæcal masses in the large intestine is another unfavorable factor because on the one hand their presence hinders the rapid passage of the contents, and on the other, it adds to the mechanical injury of the suture line. All these difficulties are magnified many times in the presence of obstruction, the usual complication of sigmoid cancer. In these cases the bowel cannot be properly evacuated before the operation, and the retention of fæcal matter further adds to the infectiveness of the bowel contents. This together with the great difference in the lumen of the bowel above and below the site of obstruction constitute additional difficulties and hazards in operative work. When total obstruction is present the bowel becomes enormously distended with gas and fluid contents, the bowel wall though apparently intact is permeable to bacteria, it is friable and tears easily. The resistance of the patient is lowered by the stercoræmia.

In operative work upon sigmoid cancer, attention should be paid to the question of fæcal load in the bowel. In the presence of a complete obstruction the radical removal of the tumor is postponed until a more favorable moment. One must in the meanwhile be content with creation of a temporary fistula. This is best made in the cæcum so as not to interfere with subsequent procedures. There is no objection to a primary end-to-end anastomosis after resection, provided the bowel has been thoroughly cleansed before the operation. For the cases which lie between these two extremes, in other words for cases in which a complete evacuation cannot be obtained, the two-stage Mikulicz procedure is preferable. The resection here is completed by formation of a fistula which is closed at a later date.

The location and the extent of the cancerous growth is another consideration to keep in mind. We shall consider as typical sigmoid cancers those growths which are located at the summit of the sigmoid coil or close to it, or at any rate, tumors so located that after their removal an end-to-end anastomosis without undue tension is possible. In view of the difficulties inherent to colon suture, even the slightest tension must be avoided. It can compromise the end-to-end suture as well as the double barrel flint formation of the Mikulicz operation. For these reasons growths involving either the descending colon or the abdominal portion of the rectum present especial difficulties and do not lend themselves to the same operative procedures as do cancers of the sigmoid proper. In cases of carcinoma involving the transition to the descending colon the best procedure is to resect the entire descending colon, the splenic flexure, and the aboral half of the transverse colon, and to restore the continuity by an anastomosis of the mobile portion of the transverse colon to the sigmoid. Cancers which extend downward to involve the rectum are best attacked by the abdominosacral route. However, we shall here consider those cases only which are limited to the mobile portion of the sigmoid bowel, and which are amenable to resection and to end-to-end anastomosis without undue tension.

The previously mentioned danger of suture line insecurity together with the handling of the distended bowel in obstructive cases resulted in peritonitis which was responsible for the terrific mortality record of the older literature. This complication can be to a great extent eliminated by the proper choice of the time of resection, by the proper choice of the site and extent of resection, by the proper method of closure of bowel

[1]Translated by George Halperin, M.D., Chicago.

stumps, and above all, by the introduction of the method of extraperitoneal fixation of the suture line after resection. This method, however, is not applicable in most localizations of the cancer of the large intestine. Tumors of the cæcum, of the ascending colon, of the hepatic flexure, and of the proximal portion of the transverse colon preclude the use of this method. They are best treated by a blind closure of the colonic stump and the implantation of the small intestine into the transverse colon end-to-side. Neither is the method of extraperitoneal transposition of the stump to be recommended in operations on tumors involving the transverse colon. It may lead to angulation or, as I saw it in one case, to strangulation of a loop of the small intestine over the transverse colon which was fixed to the abdominal wall. On the other hand, the method is applicable both in cases of carcinoma of the splenic flexure and of the descending colon in which a circular anastomosis between the sigmoid and the transverse colon can be made after resection, and in carcinomata of the sigmoid itself. In the last mentioned group one need not fear angulation or undue tension. The use of the method insures against the grave consequences of a leaky suture line. It is readily conceded that drainage in the vicinity of the suture line endangers its security; perhaps to a great extent it may be responsible for its insufficiency. On the other hand, however, it mitigates against its very danger and renders the operative procedure safe.

The second grave danger is that of recurrence. In the absence of mesenteric involvement and in the absence of invasion of neighboring tissue, this danger is relatively not great. Generally speaking, lymph node, liver, peritoneal and bone metastases are much more rarely seen than, for example, in gastric cancer. In every case, resection of the bowel should be carried out as far away from the seat of growth as possible, and, in the event of mesenteric and lymph node involvement, the latter should be widely excised. Demonstrable involvement of mesenteric lymph nodes seriously compromises the prognosis.

PREPARATION OF THE PATIENT

Thorough cleansing of the bowel is the principal point in the preparation of the patient. This of course, is possible only in cases not complicated by high grade obstruction. Cases with complete or almost complete obstruction are treated by a preliminary cæcal fistula formation. The use of cathartics in high grade obstruction is contraindicated. It causes exacerbation of the colic-like pains and may lead to much graver consequences, such as complete obstruction or rupture of a decubitus ulcer in the bowel wall above the obstruction. When passage of flatus and fæces is not interfered with, medicinal treatment is indicated. Castor oil in a single massive dose of 30 grams can be given 2 or 3 days before the operation, and if necessary may be repeated on successive days. One should, however, guard against exhausting the patient by heroic purgation. The patient should receive a fluid diet, spare in residue and rich in nourishment. It is wise to postpone the operation for a few days if the patient appears to be exhausted by the purgation. Proper results can be accomplished by rest, by proper diet, enemas and laxatives. Catharsis should be finished not less than 24 hours before the operation. A tepid water enema is given on the eve before. I consider the use of opiates both before and after operation superfluous, in some respects even injurious. On the eve of operation the patient receives a mild hypnotic. All nourishment and fluids are withdrawn 6 hours before the operation and morphine in a dose of 1 to 3 centigrams, according to the size and condition of the patient, is given one-half hour before the operation. If a fæcal fistula is present, it is utilized for washing out the bowel.

ANÆSTHESIA

I prefer ether anæsthesia induced by ethyl chloride. The operation, however, can be done under local anæsthesia especially in cases with a freely movable tumor, perhaps with a very short general anæsthesia during the search for the sigmoid. In difficult cases requiring freeing of adhesions, removal of organs such as the small intestine, the ovary, the uterus, requiring dissection from the posterior abdominal wall, or resection beyond the limits of the sigmoid, a general anæsthesia is necessary. When an objection to general anæsthesia exists, these difficult cases may be operated upon under an extensive left-sided paravertebral anæsthesia.

TECHNIQUE

Position. A dorsal recumbent position with a high pad under the buttocks is used. The tail end of the operating table is markedly elevated. The operator stands on the left, while the two assistants stand on the right side of the patient.

Isolation of the operative field. Two large towels are placed transversely, one over the symphysis so as to cover the thighs, the other across the abdomen, its lower edge reaching the level of the umbilicus. Two smaller towels are placed obliquely so as to create a rhomboid the long axis of which corresponds to Poupart's ligament and the crest of the ilium.

Incision of the abdominal wall. The incision begins four finger breadths lateral to the anterior superior spine of the ilium and parallel to Poupart's ligament and is continued in a medial direction as far as the edge of the rectus muscle. The incision is carried down to the aponeurosis of the external oblique, and subcutaneous veins and small spurting arteries are ligated. The external oblique is split in the direction of the incision, while the internal oblique and the transversalis muscles are split in the direction of their fibers and are forcibly retracted with blunt retractors. The peritoneum is split parallel to Poupart's ligament. The muscular incision can be made more ample by prolonging it backward into the fleshy portion of the internal oblique and by carrying the incision of the aponeurosis of the external oblique into the sheath of the rectus muscle. The approach is thus made much easier. Should there arise a need for a still greater exposure, the flat abdominal muscles may be cut transversely. When the transverse colon or the splenic flexure require exposure, one had better resort to a second incision. This is made parallel to the left costal border, the underlying muscles being split in the same direction.

Localization. The sigmoid is usually found close to the incision. It frequently prolapses into it. When it is not visible the small intestine is packed off to one side with the aid of a large laparotomy sponge. Elevation of the end of the table at this stage aids in exposing the operative field. The sigmoid is seized and is brought out of the peritoneal cavity. The tumor is readily delivered when it is located in the mobile portion of the sigmoid and when it is not bound down by adhesions or by a shrunken mesosigmoid. In favorable cases of this type, the peritoneal cavity is packed off and all further manipulations are carried out outside of the abdomen. When adhesions are present, one must first expose them properly in order that one may decide by direct inspection as well as by palpation the feasibility of attacking them, the possible extension of the growth into the depth, the presence of metastases in the peritoneum, of nodes in the mesentery, in the pouch of Douglas, in the vicinity of the growth, etc. Further consideration is to be given to the kind of adhesions. They may be of the type that are easily separated or, on the other hand, firmly bound to the abdominal wall or to an abdominal viscus, or embedded in an indurated mass. The presence of just such indurated tumefactions should suggest the possibility of an abscess in the vicinity of the new-growth, or an abscess the result of sigmoiditis. The unexpected, unguarded breaking into one of these may result disastrously for the patient.

Freeing of the growth. When we rule out the slender adhesions, such as result from a previous laparotomy made for an acute obstruction due to the tumor or from an inflammatory disease of the female adnexa, we must regard as serious complications all other adhesions of the new-growth to the tissue about it and to the neighboring organs and every fixation caused by mesenteric involvement. This must be clearly kept in mind before the radical procedure is decided upon, for once begun there is no backing out. The bowel may be injured, and then the radical removal of the growth and of the tissue about it must be completed in the face of every difficulty and hazard; without this an acute peritonitis is unavoidable. One must be prepared in these cases to remove a neighboring viscus, such as the uterus, the ovary, or an adherent coil of the small intestine. Tumors involving the mesosigmoid as well as those fixed to the iliac region are dissected out by incising the posterolateral peritoneal wall and working from their lateral aspect in the median direction. In the course of this dissection, one should particularly remember the ureter. The iliac vessels may come into the operative field. They should be freely exposed so as to avoid injury to them.

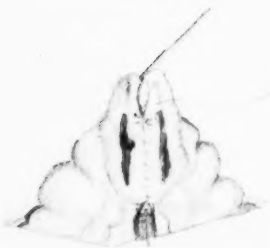
Choice of the method of resection. Upon the delivery of the tumor from the peritoneal cavity one is confronted with the question of a one-stage or two-stage method of procedure. A *conditio sine qua non* for a one-stage procedure is a thoroughly emptied bowel. When this condition does not obtain, one had better resort to the two-stage method. We shall next describe the one-stage method.

Ligation of mesosigmoid vessels. If the mesosigmoid is easily accessible then with the aid of an artery forceps a slit is made in it and sections 1.5 to 2 centimeters wide are grasped between two artery forceps to the right and to the left of the slit. These are cut between the clamps and the centrally directed portion is ligated. This is continued until the bowel to be resected is freed. When there is not sufficient room to work in, the cutting of the mesosigmoid may be made between a ligature on the one hand and the clamp on the other. Mesosigmoid ligature of course must be made central to the diseased part of the bowel as well as to the diseased lymph nodes. In difficult cases, it is best to begin with the ligation of the biggest vessel. If there are enlarged lymph glands or much fat, the vessels must be carefully dissected and doubly ligated, and only if the vessels are plainly visible and easily approached, transfixed

Fig. 1.

Fig. 2.

Fig. 3.



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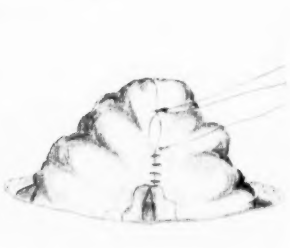

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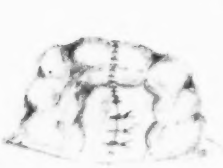

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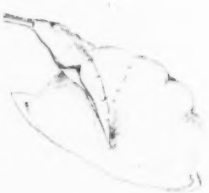

Fig. 9.

Fig. 10.

sutures may be applied. No preliminary ligations should be made in the immediate vicinity of the line of resection. Here close to the bowel the mesentery is freely incised and the bleeding vessels are separately clamped and ligated.

Resection of the involved bowel. This is done with the knife between two hard clamps. The line of incision is made oblique so that more is removed from the anti-mesenteric than from the mesenteric border. If the bowel is long enough additional soft clamps may be placed three to four finger breadths above and below the line of resection. The resection is, of course, preceded by a careful isolation of the segment to be resected and by a careful packing off of the abdominal cavity. Two extra towels are now laid on the dressings and are secured with skin clips or artery forceps. These protect the underlying isolating dressing against soiling and are to be immediately replaced when soiled. Dissection is made with a knife between two closely applied clamps.

Apposition of bowel stumps. After inspection and change of outer dressings, surrounding the bowel stumps, the clamps are removed, first from the aboral, then from the oral side. The assistant quickly grasps the mesenteric and the anti-mesenteric ends of the bowel stump with artery forceps and holds them up high. The compressed edges are now carefully separated; the adherent mucus is wiped away with small sponges; in the absence of an upper clamp, a piece of gauze is placed in the lumen; and the edges of the stump are fixed by two or three artery forceps. The two stumps are now laid side by side at the point of mesenteric attachment, and two or three interrupted catgut sutures are passed through the

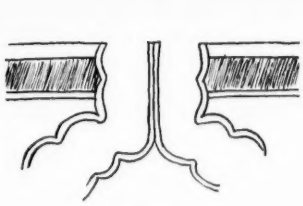

Fig. 11.

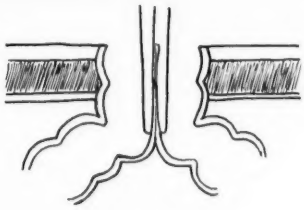

Fig. 12.

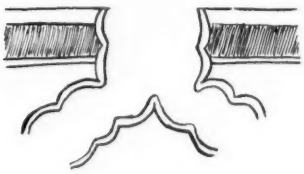

Fig. 13.

whole thickness of the intestinal wall at this point and tied within the lumen (Fig. 1). Next, a catgut suture passing through the whole thickness of the intestinal wall is placed at the antimesenteric border and is tied on the inside and left long as a stay suture.

Through-and-through suture. While the assistant holds up the antimesenteric stay suture, a through-and-through catgut suture beginning at the mesenteric border is passed through the edges, the needle passing 2 or 3 millimeters away from the border, thus bringing the stumps in apposition. When the suture has progressed to within 2 centimeters of the antimesenteric border, another single catgut suture is passed through the whole thickness of the bowel on both sides and is tied from the inside. This now serves as a new stay suture. The continuous suture is taken up once more (Fig. 4). Two centimeters further another interrupted suture is placed and then still another at the same interval and so on until two-thirds of the bowel circumference has been sutured. At this stage the running suture is tied to the last interrupted and cut. An interrupted suture is now placed on the outside so as to bring the bowel edges to within 2 to 3 millimeters, so that serous flaps will approximate each other to that extent. This suture is left long and is tied to the end of the circular through-and-through suture which has now begun on the other side at the mesenteric end (Fig. 6). At this stage of the suture the bowel is sewed from the outside, the needle is made to pass through the serosa to reappear at mucous edge to pierce the mucosa of the opposite side and come out once more 2 to 3 millimeters on serous surface of opposite side. The soft clamps and gauze sponge within the lumen are removed when suture line is within 2 to 3 centimeters of completion.

Serous suture. The two large upper sponges are now removed even if not soiled. The suture line is wiped dry, and the gloves and instruments are changed. The serous layers of the large intestines should always be sutured with interrupted sutures to make sure that each suture grasps a definite amount of tissue. The bowel serosa should preferably be sutured to bowel serosa and epiploic appendages utilized only when bowel serosa is not to be had. These appendages must be grasped by the needle close to their base. The sutures are placed 3 to 4 millimeters apart. One begins 1.5 to 2 centimeters beyond the bowel border on one side of the mesentery and ends 1.5 to 2 centimeters above the mesenteric border of the other side. Contrary to the suggestion of some surgeons, the epiploic appendages should not be removed. There is in the first place the danger of unwittingly opening into a Graser diverticulum, and on the other, these appendages may be utilized for the reinforcement of the suture line. They are secured to it by one or two serous stitches. For a serous suture I always use the finest silk and the small curved needle.

Suture of the mesentery. The breech next the bowel is closed as already mentioned with the serous suture 1.5 to 2 centimeters wide. The rest is sutured with catgut in such a way that the ligatures are covered with serosa.

Making the suture line safe. The sponges are now removed from the field of operation and from the peritoneal cavity. The peritoneal edges are grasped with forceps and the peritoneal cavity is examined for bleeding, sponges, etc. The parietal peritoneum is stitched to the sigmoid anastomosis in such a way as to leave at least four finger breadths of the oral portion of the bowel outside of the peritoneal cavity (Fig. 9). If possible, the suture line of the mesentery is included as well, though this is not so important. Aboral from the anastomosis only about one finger breadth of the bowel is thus extraperitonealized. If a cæcal fistula is present, this width would do for the oral segment as well. The peritoneum is stitched with fine interrupted silk sutures, 3 to 4 millimeters apart in the immediate vicinity of the anastomosis, elsewhere 1 to 1.5 centimeters apart. In the lower medial angle of the wound where the peritoneum was sutured to the bowel one finger breadth below the anastomosis, the parietal peritoneum is grasped not at its edge but 2 to 2.5 finger breadths back of it, and is thus sutured to

Fig. 14.

Fig. 15.

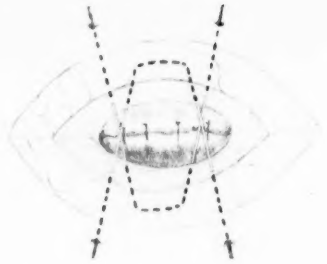

Fig. 16.

the serosa of the sigmoid. This results in a free peritoneal flap some two finger breadths in width which is to be utilized later to protect the anastomotic line against the dressings (Fig. 10). One might utilize an epiploic appendage or a piece of omentum for the same purpose, although this is best accomplished by means of the peritoneal flap just described.

The segment which lies over (orally from) the anastomosis is now designated by passing two very fine silk sutures through its serosa and muscularis. These sutures are tied loosely and left long. They indicate the location where the bowel is to be opened when the case requires it. When a cæcal fistula is present, this precaution is not necessary nor is it necessary to extraperitonealize much of the oral segment.

Dressing. Three gauze drains are used ordinarily. One is placed over the anastomotic line protected by the peritoneal flap, by an epiploic appendage or by omentum. One is placed over the bowel over the anastomosis and one to the lateral side of the bowel. In cases in which much retroperitoneal dissection is done more packing is necessary.

Suture of the abdominal wall. The abdominal wall is sutured in layers, muscles and aponeurosis with catgut, skin with silk and metal clips, sufficient room being left for the gauze drains.

Bandage. Gauze dressings are held in place by adhesive strips laid transversely across the abdomen. Cotton and a calico binder are placed over these, the latter being secured with safety pins.

MULTIPLE STAGE RESECTION

First procedure—resection. The preliminary steps—incision, ligation of mesosigmoid vessels—are the same as for the one-stage operation. When, however, because of the presence of fæces in the bowel the one-stage method appears inadvisable, one proceeds as follows:

The two limbs of the delivered sigmoid are placed parallel to one another in a flint-barrel fashion and are joined with a fine serous suture for such an extent as the case permits, at least three finger breadths. Undue tension must be avoided in order not to run the risk of angulation, perforation, etc.

The parietal peritoneum is now sutured with fine serous sutures 1.5 centimeters apart to both limbs, in a circular fashion, so that the peritoneal cavity is completely shut off at the base of the delivered bowel.

Gauze dressings are placed above and below both limbs and the wider dressing to the side of the bowel.

The abdominal wall is sutured in layers, room being left for the gauze drains and the bowel.

On completion of the skin suture the wound is covered with large dressings and the bowel is tied off with heavy silk on either side at the level at which it is to be amputated. Next, the bowel is compressed with a powerful clamp 2 to 3 centimeters above the silk ligature and is severed between the ligature and the clamp. This is best accomplished with a thermocautery.

Bandage. Same as in the one-stage operation.

Second act—crushing of the spur. This is done 2 to 3 weeks later. By this time the bowel empties itself normally through the proximal stump and the incision is to a great extent healed. Small defects in the wound corresponding to gauze drains are of no consequence. The patient is thoroughly purged a day or two before the operation and the aboral stump is thoroughly washed out by an enema or by a catheter introduced through the proximal opening of the aboral stump. The extent and the width of the partition between the two limbs is ascertained by passing the index finger into each lumen. The straight forceps is now introduced under the guidance of the finger, one blade into each lumen, so that when the two are closed the partition is grasped between them. Instead of one wide forceps one can use two small ones placed close to each other. This forceps is closed with considerable force. In a day or

two the partition dividing the two limbs necrotizes and the forceps are removed (Figs. 11 to 13). About a week later the communication between the lumina of the two limbs is explored with the finger. If it is deemed insufficient, a forceps is placed on the remaining spur in the same manner as before.

Third stage—closure of the fistula. One must wait for the complete healing of the incision and for the complete union between the bowel mucosa and the skin. When the mucosa prolapses the operation is much easier. The patient is once more purged a day before the operation and the segment of the bowel between the fistula and the anus is irrigated. This operation can easily be performed under local anæsthesia (infiltration with a one per cent novocain solution).

An incision is made in the scar between the skin and the mucosa. The edges of the latter are seized with fine artery forceps, are pulled away from the skin and are dissected from it by scalpel. The bowel is freed all around and is then closed by a number of interrupted sutures of fine catgut if possible, in a direction transverse to the long axis of the bowel (Fig. 14). On completion of suturing, the wound is wiped with a well diluted solution of tincture of iodine and a change of gloves, instruments and dressings is made. The cutaneous scar is now excised. When the latter is thin, it is sufficient to remove a width of 0.5 to 1 centimeter. The sutured bowel is dissected free from the subcutaneous fat and aponeurosis, and the first suture line is buried by means of a few serous sutures of fine silk (Fig. 15).

The skin and the aponeurosis may be mobilized if necessary and closure is accomplished by means of two U-shaped mattress sutures of stout silkworm-gut. This is the most important step in this stage of the operation. A suture on a large curved needle is made to pass say from the right side of the wound 1.5 to 2 centimeters from its edge through the skin. It is made to appear above the aponeurosis, to cross over to the opposite side, then goes below that (left) side of the aponeurosis and around the (left) side of the bowel, comes out under the (left) edge of the aponeurosis wound and returns to the opposite side passing above the aponeurosis through the subcutaneous fat and skin and emerges again 0.5 to 2 centimeters from the skin wound (right) edge. The same procedure is repeated from the opposite side, the needle being passed through the skin and subcutaneous fat of one side, then below the aponeurosis and around the side of the bowel of the opposite side, to be returned through the subcutaneous fat and skin of the original side. Each suture is tied over a roll

Fig. 17

of gauze (Fig. 17). This procedure results in bringing wide segments of soft tissue over the repaired bowel. No further suture of the skin is necessary as a rule. Eventually one or two superficial silk sutures may be added. A small gauze drain is inserted into each angle.

POSTOPERATIVE TREATMENT

After the one-stage operation. The patient is put to bed in a half sitting posture. No food is given the first day. On the second and third days tea, water, lemonade, and fruit juices are given. On the fourth and fifth days bouillon and thin soups are added. When flatus has been passed, milk, sour milk, coffee, and thicker soups may be given. From the sixth day apple sauce, paps of potatoes, of green vegetables, and gruel are added, meat being given only after the first copious bowel movement. No opiates or enemas are administered. After the second day a thick rectal tube is frequently passed. If the flatus is not passed before the third or fourth day, small enemas of oil and glycerin diluted in water not to exceed 50 cubic centimeters are administered. After the fifth or sixth day, when flatus has been passed spontaneously, cathartics, preferably castor oil, may be given by mouth.

Change of dressings. On the day following the operation the outer dressings are changed; after that every day or every other day. The gauze drains are moistened lightly with hydrogen peroxide and are not changed until the eighth day. In the presence of a profuse secretion, however, this may be done a day or two earlier. If fæcal matter appears in the wound, the dressings must be changed daily and oftener. The wound is liberally irrigated with hydrogen peroxide and the skin is protected with a thick layer of zinc paste or xeroform salve. In most cases there is very little fæcal discharge in the dressings and that soon disappears. Extensive separation of the suture line followed by profuse discharge of fæces is not frequent, and even these heal in the course of a few weeks.

The after-treatment after the first act of the two-stage operation is the same as that described for the one-stage operation.

Fæces appear in the incision on the third or fourth day. The ligature on the bowel will cut through spontaneously. However, if the patient complains of distention, the ligature may be removed from the proximal stump as early as the day after the operation. The dressings may have to be changed several times in the course of the day. The skin is protected with a heavy layer of xeroform or zinc salve. The gauze drains are changed on the eighth day. Baths are given after the second week.

The treatment after the *second act* does not differ from the preceding one. After the *third act* the dressings are changed on the day following the operation, thence once every 2 days. The drains are removed on the eighth day; the superficial skin stitches at the same time. The deep mattress sutures are left in for 10 to 12 days as long as they are not cutting through. A slight fæcal discharge may appear in the incision. If the wound is not infected and the patient is afebrile, nothing is done. Should an abscess eventually form, it is treated by timely spreading of the wound. As a rule the healing progresses smoothly. An occasional fæcal fistula closes spontaneously.

Stress must be laid upon the diet during the first week after the repair of the fistula. This should consist so far as possible of tea, lemonade, orangeade, and thin soups. The bowel is relieved by rectal tube and small enemas. Copious enemata are to be avoided. Laxatives by mouth are given on the sixth or seventh day. A more solid diet is given only after a bowel movement has been obtained.

COMPLICATIONS

Among these are collection of secretions under the drains and abscess formation in the incision. These are treated by removal of superficial and deep stitches and by separation of the wound edges. Phlegmons are treated by incision. The danger of peritonitis may be said to be almost positively excluded by the use of the method of extraperitonealization of the suture line in both operations. This is true, however, only if meticulous care is exercised at the time the tumor is delivered that proper protection be given to the peritoneum in the course of suturing, that gloves and instruments are changed often and all tension is avoided. The danger of pneumonia is less than after gastric operations.

FROM THE CLINIC OF THE WOMAN'S HOSPITAL, NEW YORK

THE "WARREN APRON" IN REPAIR OF HIGH LACERATION OF THE RECTUM ASSOCIATED WITH THIRD DEGREE LACERATION OF THE PELVIC FLOOR

LILIAN K. P. FARRAR, A.B., M.D., F.A.C.S., NEW YORK

IN 1882 Dr. J. Collins Warren presented before the American Gynecological Society a contribution entitled "A New Method of Operation for the Relief of Rupture of the Perineum through the Sphincter and Rectum." The operation has been used extensively and endorsed by surgeons for the third degree lacerations of the pelvic floor but is considered not to be applicable when the laceration extends high in the rectum. If, however, the dissection of the flap is begun high on the posterior wall of the vagina just below the cervix and is extended outside and below the sphincter ani pits on either side, the apron or flap will be sufficiently long to extend below the tear in the rectum and thus protect the wound which now lies anterior to the flap.

The technique of the operation to be described differs from the Warren operation chiefly in the outline of the flap to be used and the modern method of repairing injuries to the pelvic floor by suturing the torn urogenital diaphragm and reuniting the separated levator muscles. This method of repair has been used by the writer in 12 patients, 10 of whom have had an absolutely perfect result. Two cases required additional suturing owing to excessive catharsis in one case and a too wide separation of the legs when placed in the holding stirrups in another. In neither patient was there any injury to the flap and both had a satisfactory result. The operation is best done after a full 6 months' interval has elapsed from the last confinement, as this allows ample time for the tissues in the pelvic floor to undergo involution. The most favorable time in the month is 2 or 3 days after the cessation of the menstrual flow so that there will be time for healing before the next period begins. The bowels should be moved thoroughly the week of the operation, preferably with castor oil (1 ounce) given 4 and 2 days before the operation, and a high enema the day of the operation—6 to 8 hours before the time set for the repair. A limited diet with little residue should be given on the 3 days previous to the day of the operation.

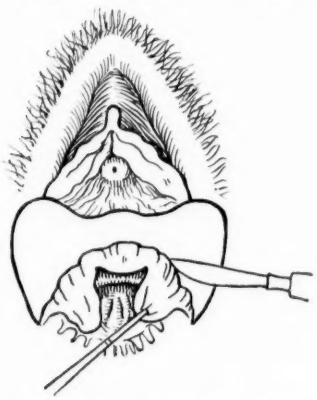

Fig. 1. Outline of "apron." (After J. Collins Warren.)

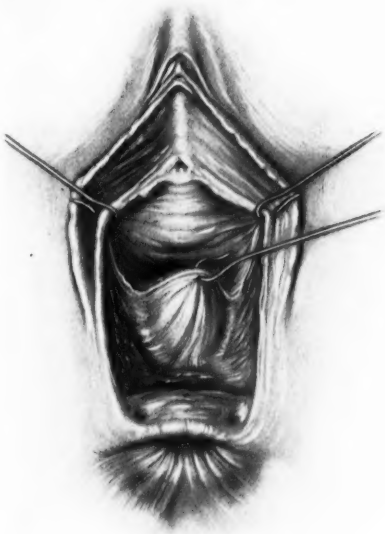

Fig. 2. Outline of operation field. (After Howard A. Kelly.)

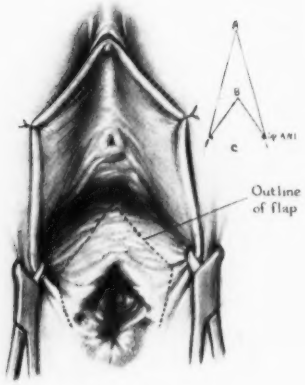

Fig. 3.

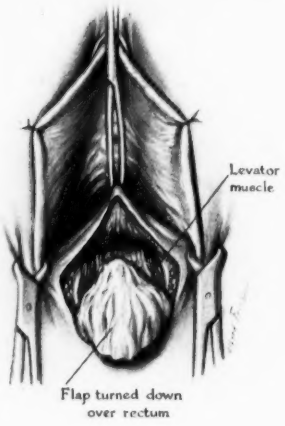

Fig. 4.

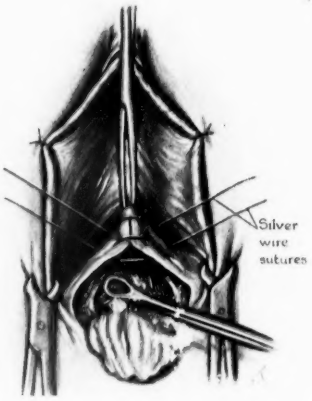

Fig. 5.

Fig. 3. Outline of apron. *A*, Dissection begun just below cervix; *B*, upper end of tear in rectum; *C*, point on imaginary line between ends of sphincter ani muscles.

Fig. 4. The flap has been turned down over the tear in the rectum.

Fig. 5. Silver wire sutures placed anterior to flap.

Before outlining the flap, the sphincter ani muscles are thoroughly stretched and a 12-inch strip of 1-inch wide iodoform gauze is packed lightly into the rectum. The technique of the operation is well shown in illustrations. Figures 1 and 2 show the Warren and Kelly flaps. Figure 3 is an outline of the apron which we use. The dissection is begun just below the cervix. *A* to *B* must equal or be a little longer than *B* to *C*. The incision must extend outside of the sphincter ani pits and a little below them. Dissect free a thick flap in the area outlined, up to the lines extending from just below the sphincter ani pit on one side to the point *B* and down to a point just below the sphincter ani pit on the other side, keeping a finger back of the flap as a guide when approaching the edge of the rectum. The flap will now hang down over the tear in the rectum and *A* will cover point *C* (Fig. 4). Carry 3 to 5 silver wire sutures anterior to the flap in the vaginal portion of the operating field (Fig. 5). The first suture should be above the apex *A*, to take the strain off the rectum when it is re-united. The second wire suture should be introduced into the mucous membrane on the left side about ⅛ inch from the margin of the denuded area and deeply enough to pick up the edge of the torn urogenital diaphragm. It should come out at the margin of the flap and catch up lightly tissue in the flap to prevent a dead space as first advised by Tait, and should be re-introduced at the right margin of the flap taking the torn edge of the diaphragm on the right and out on the mucous membrane. Successive sutures should be passed in exactly the same way until the mucocutaneous junction is reached. The anterior fibers of the levator ani muscles are then found.

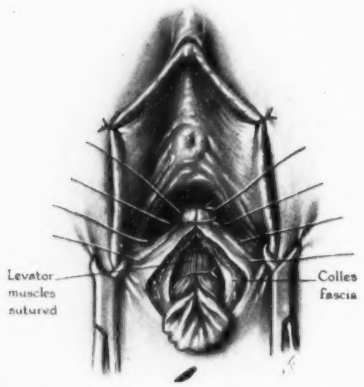

Fig. 6. Levator muscles sutured with No. 2 catgut.

The levator muscles are sutured with No. 2 catgut, and 2 to 3 silver wire sutures are passed from the skin surface of the perineum under the levator muscles (Fig. 6).

When the levator muscles are united they act as a guide to the torn sphincter muscle which should be sutured with No. 1 tanned gut, after they have been dissected out. Two wire sutures

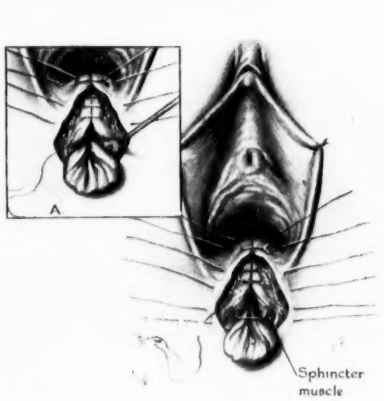

Fig. 7.

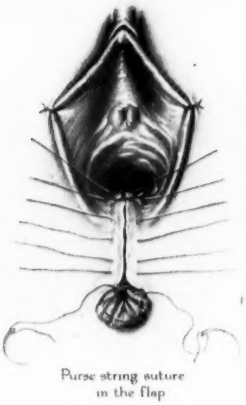

Fig. 8.

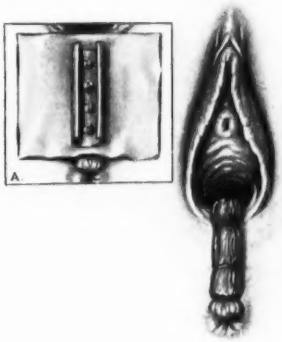

Fig. 9.

Fig. 7. Torn sphincter is sutured with No. 1. tanned gut.
Fig. 8. Purse string suture closes edges of flap which may be attached to or spread out to fit the edge of the anus

Fig. 9. All wire sutures are twisted and those in the vagina have their ends covered with a washer and shot firmly crushed.

are then passed deeply under the torn edges of the sphincter muscle. The upper edge of the sutured sphincter muscle may be sutured to the levator muscle where Luschka's fibers normally are. A continuous No. 2 tanned gut suture closes Colles' fascia and is tied later to the end of a No. 1 tanned gut suture passed subcutaneously in the skin margins, beginning at the mucocutaneous junction and ending at the anal margin (Fig. 7).

The flap now hangs in the restored anus and a purse string suture will close the edges which may be attached to or spread out to fit the edge of the anus. This flap will contract and be withdrawn into the rectum where it can be felt weeks later, only as a slight thickening on the anterior wall of the rectum (Fig. 8).

All wire sutures are now twisted and each one in the vagina has its ends covered with a washer and a shot firmly crushed. The twisted wire sutures on the skin surface are passed through a piece of perforated rubber tubing covered with thin rubber. The ends of the wires are covered with shot and the outer rubber covering is tied over the tube to keep it water tight, as in the technique which is employed by Dr. Herman Grad of the Woman's Hospital. The gauze is removed from the rectum and the knees are kept tied until the patient becomes conscious (Fig. 9).

AFTER-CARE

The perineum must be kept clean by pitcher douches of potassium permanganate solution after each urination or bowel movement. The diet should be liquids chiefly—no milk should be given, however.

The bowels are moved on the fifth day by Epsom salts repeated if necessary. Enemas are never given.

The silver wire sutures are removed on the fourteenth day under gas oxygen anæsthesia, care being taken not to stretch the pelvic floor by placing the legs in stirrups.

The principles of the repair of the pelvic floor have been taught by Emmet, Tait, Marcy, Watkins, and Ward; the anatomy demonstrated by Edouard Martin, Testut and Jacob, Halban and Tandler, and others; the method of repair of third degree laceration of the pelvic floor by Kelly, Watkins, Ristine, and Noble. So completely has this been done, that one can only assemble the technique to fit each individual case, keeping always in mind the importance of uniting the edges of the torn urogenital diaphragm and suturing together the levator muscles after reaching the mucocutaneous line where they normally decussate with one another before the injury. The support of the pelvic floor depends not on muscle or fascia alone, but upon the integrity of both muscle and fascia working together.

My appreciation and grateful acknowledgment are due to Dr. Howard A. Kelly for his invaluable guidance of many years and in this instance for his teaching the repair of the complete laceration of the sphincter ani muscle.

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CHRONIC DUODENAL ULCER[1]

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DUODENAL ulcer is an ever absorbing subject of contention among the profession. Some maintain that especially in its early stages, it is a medical condition and should be so treated; others urge more radical, i.e., surgical treatment. Some claim that even a positive X-ray report does not always establish the diagnosis; others base their diagnosis on the roentgenogram and on the results of laboratory tests. Some contend the symptoms are simulated by duodenitis and inflammation of a duodenal diverticulum; others stress the differentiation between ulcer and disease of the gall bladder and the appendix. Even among those who advocate early surgery there are differences of opinion as to the proper surgical procedure. As a matter of fact, each and every one of these opinions is justified and it is practically impossible to describe a definite picture or prescribe a definite course of treatment that will apply to every case. Duodenal ulcer, in short, refuses to conform to the modern trend of standardization because the human subject itself cannot be completely standardized.

This tendency to resist standardization depends on various factors. One of these is the site of the ulcer. The typical duodenal ulcer is found in the upper 3 centimeters of the anterior wall of the duodenum, and in many cases the peri-ulcerous exudate extends up to or within a short distance of the pylorus. The deepest part of the ulcer will usually be found just below the pylorus, where the acid secretion which is ejected with considerable force from the stomach produces an impact upon the duodenal mucosa at this point. Ulcer is rarely met with below the papilla of Vater, where the acid chyme is neutralized. Physiologically, the consensus of opinion seems to be that the acid in the pyloric end of the stomach stimulates the gastric and secretory functions. In the upper duodenum it controls pyloric function and the rate of the gastric excretion is regulated by the rapidity with which this acid is neutralized by the alkaline, biliary, and pancreatic secretions. According to some authorities, pathologically the acid gastric juices, either because of perverted secretion, or through lack of local resistance, or both, become the most important factor in the development of ulcer and largely confine their ravages to the duodenum.

The ulcer is usually round and varies in diameter from 1.5 to 3 centimeters or more. The base is either the submucosa, the head of the pancreas, or the thickened connective tissue (Fig. 1).

Inspection shows stippling, or a white central exudate with radiating white lines which can be likened to a wheel, the central white point representing the hub and the radiating white lines the spokes of the wheel. Not all ulcers, however, give so distinct a picture. Ulcer of the anterior wall of the duodenum, the most common site, cannot always be recognized even when the duodenum is exposed and drawn upward and partly out of the wound by traction upon the pyloric end of the stomach, because it is often covered over by organized exudate in the shape of a peritoneal sheet which may be styled pathological peritoneum, the surface of which frequently is greyish and dirty looking (Fig. 2). This may be one reason for overlooking an ulcer unless the surgeon adds careful dissection and palpation to inspection. When operating before an audience of students, I cleanse the surface of the duodenum by carefully dissecting off the covering referred to, so as definitely to demonstrate the ulcer (Fig. 3).

When the ulcer is on the posterior wall of the duodenum, its recognition is even more difficult. Here likewise we must look well and palpate well, otherwise the ulcer will be missed. The recognition of exudate in the lower portion of the free border of the gastro-hepatic (Fig. 4), lesser omentum in juxtaposition to the duodenum is a signpost that points to the site of the ulcer which, with the detection of the crater (which can be done by contacting the anterior bowel wall with the ulcer), justifies opening the duodenum. Then, as the margins of the incised walls of the duodenal wound are retracted, the ulcer will be exposed (Fig. 5). I place great value on the use of the Cameron light in these cases. In fact, by this means I am able to demonstrate the ulcer to the visitors in my clinic. Furthermore, by this technique if there is more than one ulcer present, it can be detected.

While writing this discussion I was much pleased to read of Balfour's ingenious method of determining the presence of ulcer of the posterior wall of the duodenum by incising the stomach close to the pylorus and introducing the finger into the duodenum to detect the ulcer, and immediately closing the opening. This simplifies the detection of the ulcer. Incidentally I may say I have also done this to determine the patulousness of the

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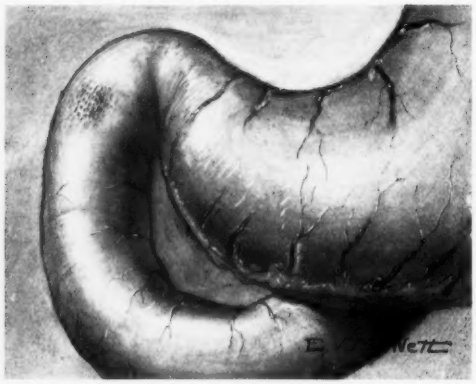

Fig. 1. Ulcer of duodenum. Stippling of surface.

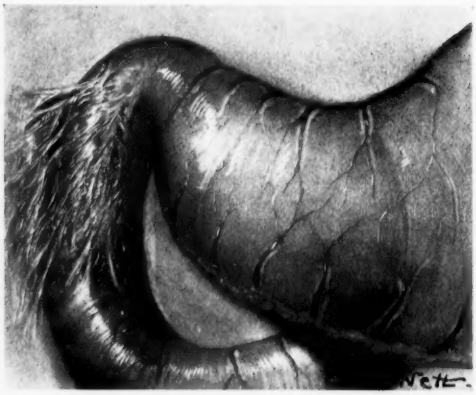

Fig. 2. Pathological band of peritoneum covering ulcer.

pylorus where I have been in doubt as to its size after making a plastic operation upon it.

W. J. Mayo has called attention to the appearance of an anæmic spot on the duodenum which may be mistaken for ulcer. The arrangement of the blood vessels of the duodenum just below the pylorus is such that if the pyloric end of the stomach is pulled forward rather firmly, as must often be done to obtain a view of the parts, this anæmic spot will appear in the duodenum just below the pyloric ring. This is very striking and may closely resemble an ulcer. The tissues apparently involved are normal to the touch and do not have the milky appearance of the peritoneal covering of a true ulcer; and stippling, an open area of organized exudate with white lines radiating therefrom, adhesions, and other abnormalities are absent. When the traction is relieved it will be seen at once that no ulcer exists. The underestimation of surgery of the stomach and duodenum and some of the unsatisfactory results reported are without doubt largely due to mistaken diagnoses and unnecessary operations for supposed but non-existing ulcer.

Duodenal ulcer is usually single, although occasionally there may be a second ulcer, so that examination for more than one ulcer is important (Fig. 6). When the ulcer is demonstrated the duodenal cap usually is easily shown since it is not apt to be surrounded by adhesions. Periduodenal adhesions due to ulcer are not nearly so frequent as are pericholecystic adhesions, the result of a diseased gall bladder. On the other hand, the duodenal deformity as shown by the roentgenogram and caused by pericholecystic adhesions, a duodenitis, or an inflamed diverticulum may simulate ulcer findings, so that the X-ray report is not always conclusive except that it shows pathology, which after all is the most important finding.

There are no known constitutional peculiarities which predispose to duodenal ulcer. The etiology I believe is infection from a more or less distant focus although the many theories offered to explain its origin show that many other factors may play a part in its pathogenesis and that these factors probably differ in different cases.

Duodenal ulcer occurs most frequently in the male sex; the reason for this preponderance is not clear. Mayo explains it on the basis of mechanics: the first or ascending portion of the duodenum in the average male ascends somewhat higher than in the average female, and as a result the alkaline secretions may rise higher and thus more readily neutralize the acid secretion in the first portion of the duodenum in women than in men.

The diagnosis of typical duodenal ulcer does not present great difficulty because the symptoms usually appear in a well-defined sequence; so well defined, in fact, that in most instances we need not hesitate to make the diagnosis from the clinical history and feel confident of having it confirmed at operation.

The typical case history of duodenal ulcer reveals years, if not a lifetime, of attacks of epigastric discomfort after meals, that is, a sense of fulness, often described as a "blown-out" feeling, and a gnawing, burning sensation, rather than pain, with acid eructations, coming on from 2 to 4 hours after meals. This distress rarely appears after breakfast, but with constant regularity after the heavier meals; the so-called hunger pain at night (about 2 a.m.) is one of the distinguishing features of the complaint. The reason for this

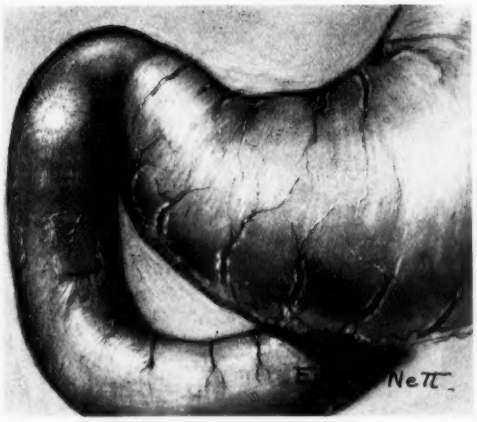

Fig. 3. Ulcer of duodenum.

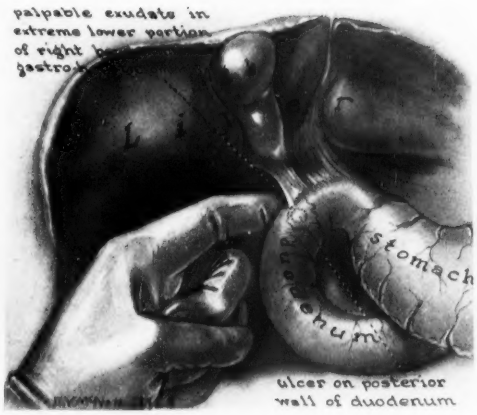

Fig. 4. Palpable exudate in extreme lower portion of right border of gastrohepatic omentum.

hunger pain has not yet been satisfactorily explained. Moynihan attributes it to changes in the muscular activity of the stomach and the duodenum stimulated by changes in the chemical quality of the chyme, especially toward the end of digestion. Food relief or subsidence of pain after eating or taking an alkali (soda) is another characteristic feature. The rhythm of duodenal ulcer then, is food, comfort, pain, and again food, comfort, pain. Mayo believes that in the greater number of cases the pain is caused by the irritant action of the acid-acrid contents on the ulcer area of the duodenum itself, heightened by the accompanying pylorospasm and gas formation, while in the remaining cases it is due to a perforating peritonitis, a complication more frequent in duodenal than in gastric ulcer, because of the thinner walls of the duodenum. The field of radiation of the pain is usually limited to the gastric and the duodenal areas.

The periodicity of these attacks with intervals of complete well-being is emphasized by all authorities. The attacks usually begin in early adult life. The patient complains of stomach trouble, of which hyperacidity is a prominent feature. This appears in about 50 per cent of the cases. The symptoms recur with increasing frequency as the patient grows older. In the later stages mechanical obstruction of the pylorus occurs.

The physical signs in duodenal ulcer are practically nil; however, in long standing cases, with much organized peri-ulcerous exudate, tenderness to deep pressure high up over the rectus muscle may be elicited. Hæmorrhage from the bowel or by mouth, as evidenced by tarry stools or the presence of blood in the vomitus, is noted in about one-third of the cases. Some patients also show a low hæmoglobin percentage. Vomiting is not considered one of the commoner symptoms of ulcer of the duodenum, but it does occur in a few cases.

The motility of the stomach is an important finding. That the motility is abnormally rapid is shown by the fact that in a good percentage of cases nothing of the test meal or the full meal is recovered in the usual time when the stomach is siphoned after the administration of the meal. This hypermotility is also demonstrated by the X-ray and the barium meal; they are thus of confirmatory rather than contributory value in the diagnosis.

Briefly stated, then, we may say that epigastric distress 3 or 4 hours after meals, relieved by eating or by alkalis; high acidity, hyperactivity of the stomach and, in some cases, vomiting and hæmorrhage, are indicative of duodenal ulcer, that is, of the typical case.

It is, of course, the atypical ulcer that presents diagnostic difficulties. It more often simulates appendicitis, especially if the appendix is high, than other conditions from which it can more or less easily be differentiated, such as gastric ulcer, cholelithiasis, cholecystitis, and chronic pancreatitis.

Chronic appendicitis frequently presents the same hunger pain as duodenal ulcer, while hyperacidity is not unusual and many cases show the same chronicity as exists in duodenal ulcer. The chief difference between the two is the freedom from discomfort in the duodenal ulcer between the attacks, while in appendicitis flatulency, gen-

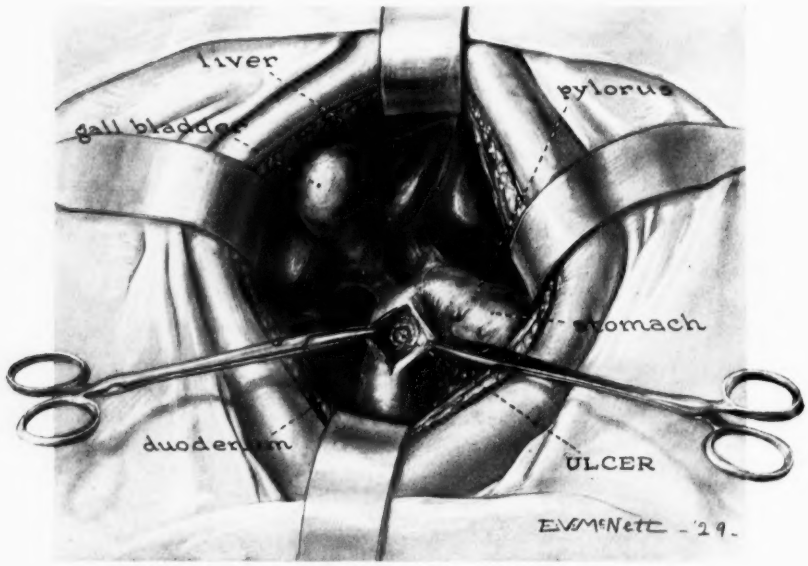

Fig. 5. Incision in anterior wall of duodenum to show ulcer on posterior wall.

eral abdominal discomfort and lower abdominal discomfort, and sometimes pain, are apt to be constantly present. But the patients with "appendiceal indigestion" usually suffer more pain after certain kinds of food, especially starchy food and red meats. The pain, however, is usually not so severe as in duodenal ulcer and the fact that it radiates downward is one of the principal points in the differential diagnosis. In appendicitis exercise frequently increases the local discomfort, which is not true of duodenal ulcer. In fact, the appendix is found diseased in so many cases of duodenal as well as of gastric ulcer, that these peptic ulcers may be considered secondary conditions; that is to say, the result of infection from some other organ with the evidence strongly in favor of the appendix as the *corpus delicti*.

In distinguishing between gastric and duodenal ulcer, we may to some extent be guided by the time relation of the ingestion of food and the onset of the symptoms. If pain appears soon after eating, in one-half to two hours, and the food relief is not prompt, we may expect to find a gastric rather than a duodenal ulcer. Again, the radiations of pain, if any, in duodenal ulcer are usually to the right, while in gastric ulcer they are generally to the left. The pain is also apt to be more constant than in duodenal ulcer. The rhythm of gastric ulcer is food, comfort, pain, comfort. Vomiting and hæmorrhage, usually in the form of hæmatemesis, are more frequent in gastric ulcer, while in duodenal ulcer melæna is more frequent. Seasonal variations are less common in gastric than in duodenal ulcer. The diagnosis of gastric ulcer is a most uncertain one; in fact, it can be definitely made only by X-ray examination or exposure at the operating table. Frequently the diagnosis of gastric ulcer is a myth and is not verified at operation.

The differential diagnosis of duodenal ulcer and cholelithiasis presents more difficulty, but care in taking the history will usually enable the experienced clinician to forecast the true state of affairs. The diagnosis is oftentimes uncertain when adhesions exist between the gall bladder and the stomach and duodenum, or when gall stones have been pushed toward the duodenum; and since hyperacidity is also a symptom of gall-stone disease, it adds to the confusion. On the whole, however, cholelithiasis is marked by such severe colic-like pain with sudden and unaccountable onset, and almost as sudden and mysterious cessation, that recognition, as a rule, should be easy. Lavage will frequently cut short an attack of biliary colic, but will have no influence on the pain of a duodenal ulcer.

Pain in cholecystitis is sudden and usually severe, with a wide field of radiation, and comes with no regularity as to time. It is rarely caused by food; however, food, by increasing gastric

peristalsis when there are adhesions, particularly to the gall bladder, will cause pain.

The chronic gall-stone case, with impacted stone, ulceration and adhesions, and the absence of jaundice, in which gastric symptoms such as gas, vomiting, burning, distress, sour eructation, and impaired appetite predominate, and pain is moderate and follows the taking of food, is too often mistakenly diagnosed ulcer; while duodenal ulcer, if there is an early history of irregular attacks of sudden, sharp, intense pain, peritonitis, or acute spasm, the absence of obstruction or hyperacidity and the presence of gas, vomiting or sour eructation, is usually mistaken for gall stone.

Symptoms similar to those of chronic pancreatitis or some pancreatic involvement, such as peripancreatic lymphangitis, are not rarely met with in duodenal ulcer. This is not surprising in view of the close relationship existing between the duodenum and the pancreas and the frequent infiltration of ulcer into the pancreas itself, as well as the close intercommunication between the pancreatic and duodenal lymphatics. For example, loss of weight and strength, pain in the back, a fairly constant clinical feature of chronic pancreatitis, is recorded in a number of cases of ulcer. The character of the pain in chronic pancreatitis is moderate, as it is in the majority of duodenal ulcer cases, and there is the same epigastric oppression. A valuable distinguishing feature of pancreatic disease, however, is that the pain has no definite relation to eating or drinking or the kind of food taken.

Duodenitis is by many regarded as a very early stage of ulcer and is not easily differentiated from actual ulcer. According to Judd, it is the only lesion found in a surprisingly large number of cases giving a long and typical history and positive roentgenogram. Inflammation of a duodenal diverticulum likewise presents a syndrome scarcely distinguishable from ulcer, although X-ray study should demonstrate the presence of a diverticulum.

Malignant neoplasms of the intestines, in their early stages, sometimes simulate the symptoms of duodenal ulcer, but careful inquiry will usually elicit the fact that the attacks of pain, though presenting the same periodicity as in duodenal ulcer, bear no relation to food, neither in their onset nor in the relief of symptoms. In the atypical ulcer, however, nothing short of X-ray examination or incision and inspection will enable us definitely to determine the nature of the lesion.

Unlike gastric ulcer, duodenal ulcer rarely undergoes carcinomatous degeneration. Perforation is comparatively common in duodenal ulcer but fortunately the contents of the duodenum are

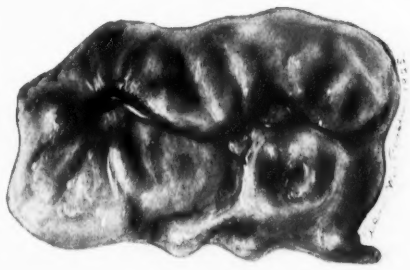

Fig. 6. Duodenal ulcers just beyond pylorus.

relatively sterile and small in amount, thus favoring plastic protection. W. J. Mayo calls attention to the fact that acute perforation of the duodenum is sometimes diagnosed perforative appendicitis and that a careful examination of the appendix in some cases of septic peritonitis from supposed appendiceal perforation would show that its peritoneal surface only is involved and that the lesion is in the duodenum. I have seen cases having all the earmarks of a perforative peptic ulcer, the sudden onset of most atrocious abdominal pain appearing like lightning out of a clear sky and in a short time followed by general board-like rigidity of the abdominal wall, and upon opening the abdomen high up I have been surprised to find the appendix perforated at or near the base. Again in cases of perforated ulcer that were not seen until several hours after the occurrence of the perforation, so that the spilled visceral contents had gravitated to the right lower abdomen by way of the external paracolic groove, I have operated, believing the condition to be due to appendicitis, to find a perforated ulcer.

Hæmorrhage in duodenal ulcer is usually recognized from the appearance of the patient and the history; however, this does not always apply, especially when the history is not typical. Confusion may arise in the differential diagnosis between hæmorrhage in duodenal ulcer, early Banti's disease, and an ulcerative œsophageal varix. It is difficult, in fact impossible, to estimate the frequency of hæmorrhage in duodenal ulcer because of the causes of bleeding to which I will refer. It is certainly true that only a small proportion of the bleeding cases come under the surgeon's notice. When in doubt, the patient's condition being good, it is my practice to open the abdomen to settle the question; at the same time, if the lesion can be corrected mechanically, I of course do so. There is a difference of opinion whether the

patient should be operated upon immediately or allowed to recover from the effects of the hæmorrhage. This will have to be decided in the individual case; however, it has been my recent practice to operate in cases in which the red blood count is not below 3,500,000, the hæmoglobin correspondingly good, and the diagnosis as nearly certain as can be. Following this course I have had good results and see no reason for not continuing this practice, but it goes without saying, with a display of good judgment. In my experience the operative mortality of a bleeding duodenal ulcer is very low, and, if surgical measures were always resorted to sufficiently early, the general mortality would be still lower. In the case of hæmorrhage from a gastric ulcer, however, we are dealing with a different proposition, as the condition is more serious and the surgery more extensive.

Obstruction of the pylorus is not an uncommon condition in the old ulcer patient. It was formerly believed to be due to a gastric ulcer, but, since operations for duodenal ulcer have become increasingly frequent, it has been shown to be due to the peri-ulcerous exudate of the latter. Pyloric obstruction is readily diagnosed by means of the X-ray, but a very simple test is to give an evening meal of raisins and wash out the stomach in the early morning before breakfast, when if raisin skins are recovered obstruction is self-evident. Giving a full meal and washing out the stomach several hours later will also show obstruction if the meal is recovered.

Although it is generally said that the question of treatment of chronic duodenal ulcer is not settled, I feel that the results of surgical treatment are, as a rule, most satisfactory. I believe that the gastroenterologist, the roentgenologist, the internist, and certain surgeons, who lack confidence in their work, are to a great extent responsible for the doubt as to the good accomplished by operative as against medical, treatment. Personally, I can say, the longer I practice surgery, the more confidence I have in its efficacy and the less in the medical treatment of chronic ulcer. The place which I give to the medical treatment of chronic ulcer is before the diagnosis is definitely established and after recovery from operation. This statement is based on a study of the non-perforative as well as the perforative ulcers on which I have operated. Nearly all of these patients have had medical treatment for years before they came to operation. It is a reflection on the profession that so many people, who many times have been pronounced cured of ulcer, die from perforation or hæmorrhage. It is claimed that hæmorrhage from an acute ulcer can be cured under medical treatment. This may be true for a large number of cases but not for all. It is also stated that recovery from hæmorrhage due to chronic ulcer takes place in the majority of instances. We all know of deaths due to hæmorrhage from acute ulcer and I have seen a number of cases of chronic bleeding ulcers that were medically treated to death. What I have just said is neither to discountenance medical treatment nor unduly to praise surgical treatment, but to give to each its proper merit. Medical treatment may often prove merely temporizing, to say the least. A good working rule is that the ulcer patient who fails to show decided improvement after one or two series of medical treatments should be confronted with the advisability of surgery.

Surgery in duodenal ulcer is not so urgent, outside of the accidents, perforation, hæmorrhage, and so forth, as it is in gastric ulcer, chiefly because of the risk of cancer in the latter which is rare in duodenal ulcer.

The type of surgery will, of course, depend on the personal preference of the surgeon and on the presenting conditions. While gastrojejunostomy plays a prominent rôle as a surgical procedure it is not the only one at the disposal of the surgeon. According to the exigencies of the case, such as size and location of the ulcer and other concomitant conditions, he may merely excise the ulcer, or do a pylorectomy or a pyloroplasty or even a subtotal gastrectomy. Indeed, wide resection was at one time and to some extent is still strongly advocated, especially among European surgeons. It may have something in its favor, but until sufficient data are at hand to prove that the more radical operation reduces the incidence or obviates the development of marginal ulcer, the most serious sequel of gastrojejunostomy, there seems no very valid reason *per se* for extensive gastric resection for duodenal ulcer.

Excision of a small duodenal ulcer is the simplest and would be the ideal operation if it positively insured the patient against future ulcers, and if it were not for extensive and troublesome adhesions which may form after the operation. For these reasons it is often advisable to supplement excision by a posterior gastrojejunostomy. The small duodenal ulcer on the anterior or anterolateral wall can be treated by excision or by perforation with the cautery (Balfour operation), followed by posterior gastrojejunostomy. For a large ulcer on the anterior, anterolateral, posterior, or posterolateral wall of the duodenum, gastrojejunostomy alone may suffice; but ulcer of the

bleeding type requires excision or cauterization if possible, or a pylorectomy and a gastrojejunostomy. The results of these methods, however, are sometimes minimized by the fact that these operations do not always effectively reduce gastric acidity, or if it is reduced, the reduction, the great desideratum of the operation, is not maintained. Posterior gastrojejunostomy alone is indicated when the ulcer is located low down on the duodenum close to the head of the pancreas, as well as for ulcer obstructing the pylorus or the terminal duodenum. The latter, fortunately, is rare.

Having dwelt on some of the disadvantages of medical therapeusis, it is only fair to call attention to the complications that may follow surgery. The most unpleasant and disheartening of these is, of course, marginal ulcer, which as we all know has the same inherent possibilities of hæmorrhage and perforation as pertain to the primary condition. The incidence of marginal ulcer varies from 1 to 3 per cent or more. The cause may be faulty technique, or ulcer diathesis, that is, the persistence of a hyperchlorhydria. But whatever its cause, its incidence helps to keep the surgeon humble. The treatment of marginal ulcer is eminently surgical. The best procedure when the pylorus and duodenum are patulous is to cut out the anastomosis including the ulcer and peri-ulcerous exudate, close the opening in the stomach, and anastomose the cut proximal and distal ends of the jejunum. Otherwise the procedure would be to undo the anastomosis and to perform a gastric resection, either a sleeve operation or a subtotal gastrectomy. In the hope of avoiding this sequel I have for the past 2 years or more been making fewer gastro-enterostomies. Instead, I have been removing the anterior half of the pyloric sphincter when feasible. This can be ideally done only if the ulcer is distant enough from the pyloric ring to make possible a complete dissection, but if the peri-ulcerous exudate abuts the pylorus, the muscle cannot then be completely removed.

The complete operation entails removal of the anterior muscular wall of the upper duodenum to a distance of a little less than one-fourth of an inch from the pylorus as well as that of the muscular wall of the stomach to a distance of one-half to three-quarters of an inch proximal to the pylorus. In the small ulcer favorably located, I have simply removed the anterior half of the pyloric sphincter. In the comparatively large ulcer in which the peri-ulcerous exudate is not too extensive, I excise the ulcer, including the peri-ulcerous exudate, in addition to removing the muscle, terminating the operation by a gastroduodenostomy. I have done this in bleeding ulcer and in a few cases of acute perforated ulcer. The greater number of excisions of the anterior half of the muscle that I have made, however, have been for pylorospasm due either to gall-stone disease or to hyperchlorhydria. The results have been satisfactory. The rationale of this operation is that it provides for better intermixture of the gastric and duodenal contents. This does away with a gastro-enterostomy, which is an advantage, especially as it does not interfere with making a subsequent gastro-enterostomy should the occasion arise.

PSEUDOMUCINOUS CYSTADENOMA

Analysis of Thirty Cases in Which the Cysts Were Not Ruptured Before Operation[1]

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OVARIAN pseudomucinous cystadenomata comprise a large proportion of the ovarian cysts with which the surgeon has to deal. According to the classification, as given by MacCarty and Sistrunk, the cystadenomata include the ovarian cysts which are lined by columnar or cuboidal epithelium and which contain highly albuminous material. Those which contain serous material are unilocular, whereas those which contain soft, gelatinous material or highly mucinous fluid, that is, the pseudomucinous cysts, are multilocular and have thin walls. The gelatinous material may show a mixture of yellow, red, gray, or green, depending on the degree of hæmorrhage and on the amount of fatty material, of cellular detritus, or of cholesterol which is contained within the cyst. The epithelial lining may be hyperplastic and may be thrown into folds or papillæ which have connective tissue pedicles and which are covered with epithelium continuous with that lining the cyst. The papillary growths may be intracystic or extracystic. When seen under the microscope, the cells of the epithelial lining of the cysts may exemplify all stages of the process of secretion. Hertzler differentiated two main structural types of pseudomucinous ovarian cysts, the papillary and the glandular, and stated that the papillary type is more frequently bilateral.

The course of pseudomucinous tumors is slow. They may produce pseudomyxoma peritonæi following spontaneous rupture of the cyst or following accidental rupture at the time of operation. As a result of such rupture and of the consequent spilling of the cystic contents into the peritoneal cavity, epithelial cells may become implanted on the peritoneum and may continue to secrete. These tumors frequently are unilateral and pedunculated and grow to large dimensions. Ewing gave the occurrence of pseudomucinous cystadenoma as bilateral in 17.7 per cent of cases, whereas Lehmann estimated that 30 per cent of women with a pseudomucinous cystadenoma in one ovary will have a similar tumor in opposite ovary. The tumors consist mainly of pseudomucin.

Wilson found 144 ovarian pseudomucinous cystadenomata in a series of 331 cases of ovarian tumor in which he operated. Taylor stated that the frequency of pseudomucinous tumors is variously reckoned as from 30.6 per cent (Stuckler and Bravdes) to 53.6 per cent (Lippeot) and even to two-thirds (Pfannenstiel) of all ovarian new-growths; of these only 6.7 per cent are said to be malignant. This same author carefully reviewed 139 cases of ovarian tumor in which he had operated. He found 6 cases of benign papillary pseudomucinous cystadenoma and 5 cases of mucous carcinoma graded 1. Probably 2 to 5 per cent of pseudomucinous cystadenomata, as reckoned by different authors (14, 15), give rise to the condition of pseudomyxoma peritonæi.

Different ideas have been expressed as to the etiology of pseudomucinous ovarian cysts. MacCarty concluded, from his histological studies of ovarian cysts, that the pseudomucinous cysts develop, by hyperplasia of the lining epithelium, from simple cysts or from the stratum germinativum of the ovary. He found a small ovarian cyst with a lining which contained the many-layered epithelium of the graaffian follicle and simple cyst, the columnar epithelium of the cystadenoma, and the papilloma of the papillary cystadenoma. Goodall expressed the belief that pseudomucinous cysts not only are ovulogenic but that they also take origin from the germinal epithelium. Taylor, in a recent article, expressed the opinion that pseudomucinous cysts may perhaps be similar in ultimate origin to the serous tumors of the ovary, but that there are elements in their etiology and pathology which justify their being considered as constituting an entity. He suggested that they may be of teratomatous origin. Mueller also expressed the belief that pseudomucinous cystadenomata are of teratomatous origin.

Usually when these ovarian cysts are removed at operation with an intact capsule, the prognosis for cure is excellent. Occasionally there is recurrence, even when the capsule is kept intact, sometimes after many years. Olshausen reported a recurrence under such circumstances 17 years after the removal of the ovarian tumor, and Lewis reported one 22 years after primary operation. Mayfield, in a detailed analysis of 100 cases of

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papillary cystadenoma, found 6 cases in which recurrence took place and in which the capsules of the cysts were said to have been intact at the time of operation. The presence of malignant tissue in the primary cystadenoma may be a significant factor in such recurrences.

ANALYSIS OF CASES

The histories of 30 unselected cases in which pseudomucinous cystadenomata of the ovary were surgically removed at The Mayo Clinic within the last 6 years were reviewed. The cysts were unruptured before operation. This number was chosen so that a comparison could be made with a study, given in another paper (11), of 30 cases of ruptured pseudomucinous cystadenoma which had produced pseudomyxoma peritonæi. A questionnaire was sent to the 30 patients regarding their health at the time when they received the questionnaire. Replies were obtained from all but 4. The material was treated on a basis of percentage because it was thought that by this means the relative values could be more clearly brought out.

The average age of the patients was 48.4 years. The youngest patient was aged 24 years and the oldest, 71 years. The greatest number, or 11, were in the sixth decade of life; 7 were in the fourth, 6 in the fifth, and 4 in the seventh decades. In 8 of the cases the tumors were malignant, as determined by microscopic examination. The average age of the patients with benign conditions was 46 years, and the average of those with malignant conditions, 55 years. Seventy-three per cent of all the patients were aged more than 40 years. Sixty-three and six-tenths per cent of the patients with benign conditions and 87.5 per cent of those with malignant conditions were beyond the age of 40 years. In 2 cases there was a family history of malignancy, but in neither of these cases was the cystadenoma malignant. Twenty-five of the patients had been married and 24 of them had had children. Twelve were past the menopause and 6 of these had had recent recurrences of uterine bleeding. In 72.3 per cent of 18 cases in which the menstrual history was given definitely, menstruation was normal, and in 27.7 per cent there was a history of some irregularity previous to the menopause.

The symptoms in most cases were of gradual onset and included enlargement of the abdomen, increase in intra-abdominal pressure, a sensation of bearing down, urinary frequency, and dysuria. The complaint of increase in size of the abdomen was noted in 16 (53.3 per cent) of the cases. Abdominal pain, mostly in the lower quadrants, was complained of by 13 (43.3 per cent) of the patients; in 3 patients, the pain was acute.

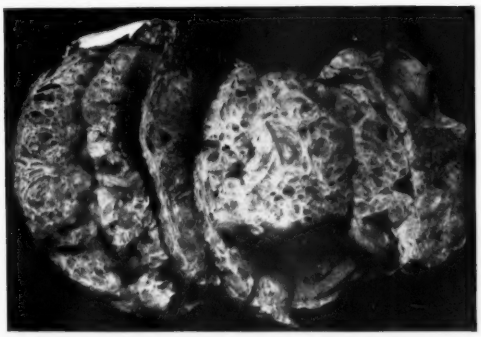

Fig. 1. Pseudomucinous cystadenoma showing typical honeycomb appearance.

The duration of symptoms at the time the patients presented themselves at the clinic was given fairly definitely in 23 cases and averaged 20.2 months. Sixteen of these patients had benign cystadenomata, and the average duration of symptoms was more than 2 years (25.8 months). In 7 patients who had ovarian tumors that on microscopic examination were found to be malignant, the average duration of symptoms was only 7.7 months.

General examination revealed pelvic or pelvic and abdominal tumors which presented cystic characteristics in most instances. One of these tumors reached from the pubis to the xiphoid process of the sternum. Marked anæmia was not present in any of the cases; the reading for hæmoglobin usually was between 60 and 70 per cent (Dare).

At operation, either one or both ovaries were removed. In several cases the uterus, tubes, or appendix, with associated fibromyomata or inflammatory disease and the affected organs were removed. In one case, cholecystectomy for cholelithiasis was performed a few days after laparotomy. In 7 cases, tenacious adhesions caused the cyst to be adherent to the surrounding structures. In 3 cases there was marked gross evidence of old pelvic inflammatory disease. In 3 other cases, notable quantities of straw colored, ascitic fluid were present; the quantity amounted to several liters in one case. The pseudomucinous cysts varied in size from that of a mass 6 millimeters in diameter to that of a mass larger than a normal pregnant uterus. Most of them were from 15 to 30 centimeters in diameter. In several of the cases in which the cysts were larger, marked thickening and injection of the parietal and

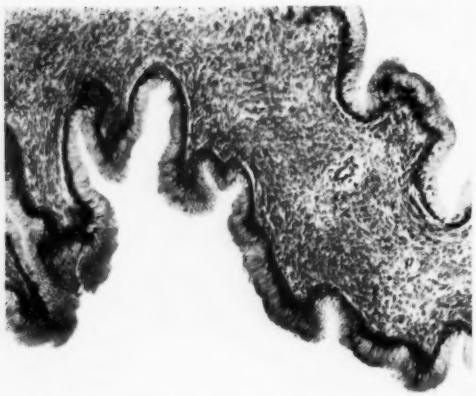

Fig. 2. Lining of pseudomucinous cystadenoma showing columnar type of lining epithelium.

visceral peritoneum were to be seen. The ovarian pedicle was long in several cases and it was definitely twisted in two. In 4 cases, the pseudomucinous cystadenoma was unavoidably ruptured in the separation of adhesions and removal of the cyst (Figs. 1 and 2). In 2 of these cases cysts were microscopically malignant. In the cases in which the cysts were ruptured, the spilled cystic content was removed as cleanly as possible and the region was thoroughly washed with physiologic solution of sodium chloride. In 6 cases, the uterus contained single or multiple fibromyomata. In one case of malignant cystadenoma, there was a metastatic carcinomatous nodule in the body of the uterus. The patient in this case was 57 years old; she had had a foul, bloody, vaginal discharge for 7 months previous to operation (Fig. 3).

The right and the left ovaries were affected in about equal proportion in cases in which involvement was unilateral. The condition of both ovaries was definitely known in 25 cases. Involvement with pseudomucinous cystadenoma was bilateral in 22.2 per cent of the cases in which the process was found to be benign on microscopic examination, and in 28 per cent of those in which it was found to be malignant. This gave bilateral involvement in 24 per cent of the cases.

In 22 (73.3 per cent) of the 30 cases, the pseudomucinous cystadenoma was found to be benign on microscopic examination, and in 8 (26.7 per cent), malignant. In the group of patients in whom the process was benign, 6 had one normal or atrophic ovary. In these patients, the other ovary contained a pseudomucinous cyst in 6 cases, a corpus luteum cyst in 2 cases, and a simple cyst in 4 cases. Chocolate colored material was in one of these cysts. In another case, the simple cyst was associated with chronic oophoritis. In 1 case, there was papillary pseudomucinous cystadenoma in one ovary, and the other ovary was the site of chronic oophoritis associated with the presence of fibrous papillomata covered with epithelium.

In the group of patients who harbored a malignant process in one ovary, 2 had dermoid cysts in the other ovary, and in 2 the other ovary was senile or atrophic. In one woman, who had a papillary carcinomatous pseudomucinous cystadenoma in one ovary there was chronic cystic oophoritis in the other. In 1 case one of the ovaries was the site of malignant papillomatous pseudomucinous cystadenoma and in the other ovary, a pseudomucinous cyst but a malignant condition was not found.

Papillomata were seen on gross examination in 6 (27.2 per cent) of the benign pseudomucinous cystadenomata and in all of the malignant pseudomucinous cystadenomata. Broders is of the opinion that all growths which on microscopic examination are found to be papillary fibromyomata covered with layers of columnar epithelium are malignant. Unfortunately, in only 2 of the cases in which a benign papillomatous condition involved one ovary was the condition of the other ovary definitely known. In both of these cases bilateral pseudomucinous tumors were present.

There were no postoperative deaths in hospital in the 30 cases. One of the patients with a benign condition had received roentgen-ray treatment pre-operatively before coming to the clinic. Another woman, aged 71 years, who had a bilateral papillary pseudomucinous cystadenoma, was advised to have roentgen-ray and radium treatment postoperatively. Five of the patients with malignant pseudomucinous cystadenomata had roentgen-ray and radium treatment postoperatively.

Recent reports have been received concerning the health of 18 of the 22 patients who had benign conditions and concerning all 8 of those who had malignant conditions. The interval since operation in the group with benign conditions varied from 5 months to 6 years, and 15 of the 18 patients were in excellent health and had no reason to believe that the pathological condition had recurred. In 3 cases, however, the state of health was questionable. One woman, aged 56 years, who had undergone right oophorectomy for pseudomucinous cystadenoma 5 years and 4 months previous to the time when she answered our inquiry had gained 90 pounds in weight. She was not sure whether or not there was recurrence of

the growth. Another patient, aged 36 years, who 4 years and 7 months before she answered the questionnaire had submitted to bilateral partial oophorectomy for papillary pseudomucinous cystadenoma of one ovary and chronic oophoritis with papillomata of the other ovary, wrote that she had fluid in the abdomen. This probably denotes recurrence of the papillary tumor. A third patient, aged 40 years, who 3 years and 6 months before she wrote had undergone right oophorectomy for papillary pseudomucinous cystadenoma gave indefinite replies to the questionnaire. She affirmed that her old symptoms had returned and that she wished another operation.

The outcome in the 8 cases in which malignant conditions were present has not been so fortunate. The intervals since operation in this group have varied from 2 to 5 years. Two of the patients are dead. One, aged 59 years, died 2 years and 4 months after operation. The other, aged 61 years, died 3 years and 7 months after operation, apparently from recurrence of the disease; she underwent left salpingo-oophorectomy for a papillary carcinomatous cystadenoma in the ovary and had not received roentgen-ray and radium treatment after operation.

Five of the other women are in excellent health and have no reason to believe that the pathological condition has recurred. One patient, aged 57 years, who was operated on 4 years before she answered our inquiry wrote that she is confined to bed part of the time but that there is no noticeable enlargement of the abdomen. She submitted to panhysterectomy for carcinomatous papillary pseudomucinous cystadenoma of the right ovary, 7 centimeters in diameter, within which was a solid area of carcinoma 2 centimeters in diameter. A small quantity of the content of the cyst was spilled when the cyst was removed from the abdomen. The left ovary was normal. Also this patient harbored within the body of the uterus near the internal os, a unique annular papillary carcinoma which was thought to have been caused by extension of the ovarian malignant growth.

COMMENT

In comparing the results of this study with those of the 30 cases of pseudomyxoma peritonæi of ovarian origin it is seen that 50 per cent of the patients with pseudomyxoma peritonæi had bilateral pseudomucinous cystadenomata of the ovaries, whereas the involvement was bilateral in only 24 per cent of the present series, in which the cysts were not ruptured. Also, malignant conditions were present in only 26.7 per cent of the cases in which the cysts were not ruptured as against 43.3 per cent of the cases in which the cysts were ruptured and in which pseudomyxoma peritonæi developed. Odd as it may seem, the average duration of symptoms before the patients came to the clinic was 20.2 months in the present series, whereas in the series in which cysts had become ruptured the duration of symptoms usually was less than a year. This may be explained partly by the greater proportion of malignant cysts in the patients whose cysts ruptured and in whom pseudomyxoma peritonæi subsequently developed. However, when a malignant condition is present in these cases, it is usually of a low grade of malignancy (grade 1 or 2 according to Broders' classification). The average ages of the patients in the two series were approximately the same, namely, 48.7 and 49.9 years respectively.

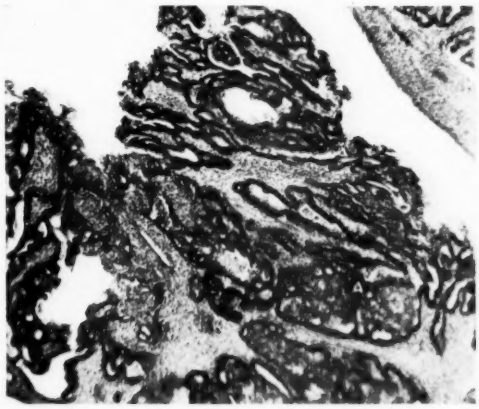

Fig. 3. Malignant pseudomucinous cystadenoma.

The prognosis is usually good when the pseudomucinous cyst is removed before rupture, but even under this favorable condition recurrence can take place. One of the patients who had a benign, papillomatous cystadenoma leads one to surmise, from her answer to the questionnaire, that she has a recurrence. In 2 other cases, recurrence seems possible. Two of the women who had malignant conditions apparently have had definite recurrence. One of these patients has died.

The treatment of patients with pseudomucinous cystadenoma is surgical. The use of roentgen-ray and radium after operation is advisable in those cases in which evidence of a malignant condition is found by microscopic examination. After menopause, the removal of both ovaries is worth while, even though only one of them appears to be involved with pseudomucinous cystadenoma. Bilateral removal is more urgent when

papillomata are seen grossly or when a malignant condition is found microscopically. If there has been postmenopausal uterine bleeding, the uterus also should be removed. In cases in which operations for bilateral pseudomucinous cystadenoma are performed before menopause, the attempt to save a portion of one ovary that may appear not to be diseased is of questionable benefit. One of the patients in the group with benign conditions, and who possibly had a recurrence, was treated in this manner. When it is necessary to save one ovary, the surgeon should give due consideration to the type of growth in the affected ovary, namely, as to whether a malignant condition or gross papillomata are present. When a pseudomucinous cystadenoma is unavoidably ruptured at the time of its removal, thereby soiling the pelvis with some of the cystic content, the spilled material should be cleanly removed as far as possible and the pelvis thoroughly washed with physiologic solution of sodium chloride. Covering of the raw surfaces with peritoneum is an important measure.

SUMMARY

Thirty cases of pseudomucinous cystadenoma of the ovary in which the cysts were not ruptured previous to operation are analyzed. The largest number of patients was in the sixth decade of life. The average age was 48.7 years. Seventy-three per cent were aged more than 40 years.

Twenty-two of the patients had tumors that were found to be benign on microscopic examination; 8 had evidence of a malignant condition in the pseudomucinous cystadenoma, as revealed by microscopic examination. The average age of the patients who had benign conditions was 46 years and the average age of those who had malignant conditions was 55 years. Sixty-three and six-tenths per cent of the patients with benign conditions and 87.5 per cent of those with malignant conditions were aged more than 40 years.

Swelling of the abdomen and pain were the most common symptoms. They were usually of gradual onset. The average duration of symptoms before the patients came to the clinic, among those with benign conditions, was 25.8 months, whereas among those with malignant conditions it was only 7.7 months.

The right or the left ovary was involved singly in about equal proportion. Bilateral involvement was present in 22.2 per cent of those cases in which microscopic examination revealed the condition to be benign and in 28 per cent of those in which the condition was similarly disclosed as malignant.

Papillomata were visible to gross inspection in all of the malignant cysts. There is a greater tendency for bilateral involvement if papillomata are present. There was no operative mortality in the group.

The prognosis usually is good but recurrence may take place even though the cyst is not ruptured at the time of its removal. The removal of both ovaries is indicated if the women are past the menopause and especially if a malignant condition has been noted at microscopic examination or if gross papillomata are present. The uterus should be removed if there has been postmenopausal bleeding. The use of roentgen-ray and radium after operation is advisable in patients in whom evidence of a malignant condition in the cystadenoma has been found on microscopic examination. If a malignant condition is found it usually is of grade 1 or 2, according to Broders' classification.

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CONGENITAL DISLOCATION OF THE HIP

Diagnosis and a New Method of Treatment in Infancy[1]

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THE subject of congenital dislocation of the hip is one of extreme importance, first on account of the great deformity and disability which are the fate in untreated cases; second, the low percentage of cures and the unsatisfactory results of the so-called conservative treatment. By conservative treatment I mean the attempted reduction of the dislocated head under an anæsthetic and the application of a plaster-of-Paris cast. According to present practice, conservative treatment is started late, rarely before the third year of life. The poor results are due to the malformations of the head, the neck, and the acetabulum during the period of rapid growth in early childhood; to the constriction of the capsule which often makes it impossible to pass the head through, while making the manipulative reduction; and to the damage to the bony structures which may occur during the operative manipulation.

Galloway states that in the hip joints he has opened, it was clearly a physical impossibility to pass the head through in at least 95 per cent of the cases.

In opening a symposium on congenital hip dislocation at the annual meeting of the American Orthopedic Association held in Washington in May, 1928, Allison says: "In the last 10 years a recognition of the possible damage done to the growing upper femoral epiphysis by manipulation has been slowly established. This fact is of great importance. It is realized also that the growing upper end of the femur may be seriously damaged by the force applied in attempts at the time of the manipulative reduction."

Farrell says: "I am going to agree with Dr. Allison that the results in congenital hips throughout the country are far from satisfactory, and that the percentage of cures is very low, much too low for a condition that is as common as congenital hip."

Gill says: "The obvious reason for early reduction is that growth and development so change the upper end of the femur (I would also add the acetabulum) that reduction becomes increasingly difficult. The constant trauma of function in the unreduced hip also produces marked changes in the growing epiphysis."

To all these early pathological changes must be added those that come on later in life: Osteochondritic and severe arthritic changes (Kreuz, Scholz, Calot): A case has been reported in which a perfect anatomical cure had been achieved, but 7 years later an X-ray examination revealed the total absorption of the femoral head. These poor results have started such a wave of operative procedures that some men will treat their cases only by open operation.

In this relation I will again quote Farrell: "Personally I am rapidly coming to the conclusion that open operation is much preferable to manipulation, unless the reduction can be done with very little trauma." Allison says: "One fact stands out clearly in a discussion of this question, namely: It will be by open operation, by early operation, and by gentle operation that the results in congenital dislocation will be improved."

Farrell, von Lackum, and Smith state: "We believe that personally every congenital dislocation of the hip within a reasonable age limit can be reduced by open operation, and in this way improved. The results in this series of cases compel us to believe that a much larger percentage should be reduced by open operation than was so treated."

Mr. Harry Platt, of Manchester, England, says: "At the present time there is a growing dissatisfaction with the anatomical results of closed reduction, and we appear to be on the eve of a revival of the open operation in young children."

Stephens reviewed the end-result of the treatment of congenital hip dislocation. The cases embodied in the report were all treated as indoor patients at the Hospital for Ruptured and Crippled during a period of 20 years. He says, "From this we might infer that the percentage of cures might be even less than fifteen." And further, "If the percentage of good results is not markedly increased, then we might conclude that our methods of treatment have been unsatisfactory and should be changed."

As a last authority I will quote Dr. David Silver, discussing Dr. Allison's paper: "Hope of future improvement, Dr. Allison said if I understand him correctly, is to be looked for in open

[1]Read before the section of Pediatrics of the New York Academy of Medicine, May 9, 1929.

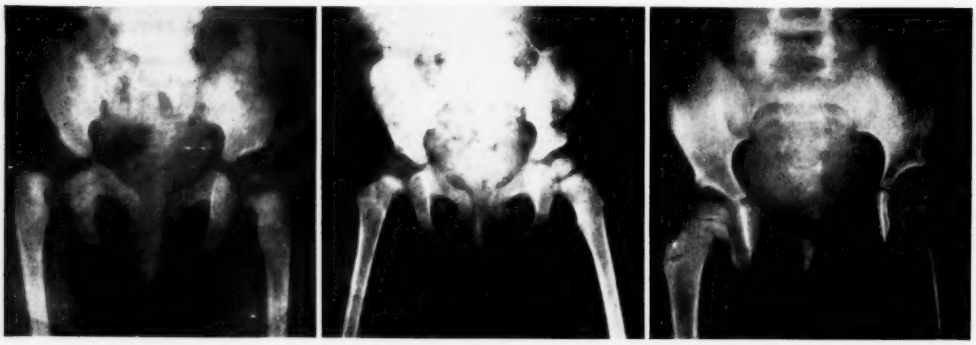

Fig. 1. Roentgenograms of Case 1 before treatment, at the end of treatment, and 4 years later. Note the late ossification of the dislocated head.

operation. This statement appears to me to be absolutely wrong. Hope for future improvement lies in early recognition. Since structural adaptation becomes increasingly greater as the child grows, and hence the degree of function to be looked for, it becomes correspondingly less, whatever the method of treatment used, would it not be wiser for us to devote less time to the discussion of the relative methods of the closed and open methods, and concentrate our energies on efforts to secure diagnosis as early as possible?"

I wish to tell how to make the diagnosis in infancy, and having made it, how to apply a treatment that will avoid all deformities, complications, and the long and painful treatments. My own treatment, which can be applied without discomfort to infants as young as 3 or 4 months of age, will bring about a physiological restoration of the affected joint, within as short a time as 3 months. By means of this treatment anæsthesia, manipulation, open operation, and plaster-of-Paris casts are all avoided.

I will not discuss the theories advanced as to the causes of congenital dislocation of the hip. My own conviction is that there is sufficient displacement in very early life to cause pressure of the femoral head against the upper rim of the acetabulum, which pressure prevents the growth of the upper rim. Removal of this pressure is promptly followed by development of the upper rim of the acetabulum.

In the first months of life, growth and development are very active. A familiar phenomenon of birth fractures is that callus is thrown out quickly and in amazing quantity. I will demonstrate in the X-ray pictures of my 2 cured cases how bone formation begins soon after removal of the resistance which retards it.

DIAGNOSIS

Several points may be mentioned in the diagnosis of unilateral cases:

1. Habitual outward rotation of the affected leg.

2. Shortening of the affected leg. This is often seen by inspection and may be ascertained by comparative measurement of both legs from the anterior superior spine to the inner malleolus.

Another test for shortening is this: Lay the child on a hard smooth table and (a) flex both hip joints to 90 degrees; and with the knees flexed the knee of the affected leg will then be at a lower level.

(b) With hips flexed as above, fully extend the knees. In this position the shortening, which was apparent with the legs extended, becomes more marked. There is in addition tension of the tuberocrural muscles and an absence of resistance backward.

3. Fullness over the trochanter, causing an apparent widening of the pelvis on that side.

4. Abnormal mobility of the hip, especially in rotation (a very important sign).

5. Very noticeable difference in the inguinal folds. On the affected side the fold is shorter, the angle is changed (being more vertical), and the inferior inner end is higher than on the normal side.

6. Exactly the same change in the gluteal folds as in the inguinal folds.

7. The diagnosis is verified by the roentgenogram.

In the bilateral cases we find:

1. The same signs as in unilateral cases except that the inguinal and gluteal folds offer no help.

2. Habitual outward rotation of both legs.

3. The pelvis is comparatively wide.

Fig. 2. Roentgenograms of Case 2 taken before treatment, 5 weeks after brace was applied, and after 4 months of treatment. Note the late ossification of the dislocated head.

4. No lengthening of the measurements from the anterior superior spine to the external malleolus as in normal hips when both legs are forcefully abducted but instead an equal distance or even a shorter distance than if the legs were lying parallel.

5. A sort of crackling or click, which occurs spontaneously when the legs are moved, especially when they are abducted and then extended. This sign, which has been described by Hoffa, is believed to be due to the rubbing of the femur against the posterior margin of the acetabulum within a loose capsule.

6. The diagnosis is confirmed by the X-ray plate.

TREATMENT

For years I have had in mind a new form of treatment based on an entirely new principle. This treatment should be begun in earliest infancy. Without force or violence, without an anæsthetic, it is my aim gradually to replace the dislocated head in the socket by means of a pressure pad over the trochanter while the leg is held in marked abduction by means of a long hip splint. I hope thus (1) to prevent the deformities that inevitably develop; (2) to make use of the very rapid growth in infancy to aid in the formation of a socket; and (3) to reduce the dislocation without traumatism, thus avoiding the consequences of rough manipulation.

I am indebted to Dr. F. Elmer Johnson, of New York City, for the opportunity of treating my first case,[1] and I wish to compliment him for having made the diagnosis of a hip dislocation in a child 3½ months of age. A brief history of the cases follows.

[1] This case was reported and the treatment described in a paper read at the meeting of the orthopedic section of the New York Academy of Medicine, May 15, 1925.

CASE 1. J. R., a female child, aged 3½ months, was the first child of a first pregnancy which terminated in a full term, normal labor. There is no history of congenital dislocation of the hip in the family. The patient weighed 5¼ pounds at birth. Dr. Johnson noticed preternatural rotation of the right leg and 1 centimeter shortening. He made the diagnosis of congenital dislocation. The child was in such delicate health and its condition so poor, that no X-ray picture was made until 2 months later. This picture, made at the Babies' Hospital, confirmed the diagnosis. On May 7, 1924, the patient was seen by the late Dr. Frauenthal, who advised reduction and plaster-of-Paris cast for the hip. The baby, still very delicate in health, was not referred to me until the age of 7 months, when it was considered treatment might be begun. I suggested my plan to the parents. Further advice was sought and Dr. Royal Whitman examined the child. He suggested waiting 2 or more years, until the child was of an age suitable for reduction and plaster cast. When the parents told him of my plan for immediate brace treatment, he advised the parents to let me try it.

I began the treatment in this manner: A long hip splint of rustless steel was designed. This splint consisted of two circular bands to fix the pelvis and chest; two lateral bars to support the leg; to the lower end of the bars was attached a footplate with a leather anklet. This maintained the midposition of the leg, i.e., it was in neither outward nor inward rotation. The long outer bar was bent to fit the leg at 45 degrees abduction. There was no provision for traction or extension, because I deem it entirely unnecessary to subject a child to the inconvenience and irritation of the traction straps, and besides nothing is gained by their use.

In order to accomplish the gradual reduction of the dislocated head, I depend upon an adjustable pad, controlled by a wing screw about 1.5 inches long, placed directly over the trochanter. The pad pressing downward and inward, gradually and easily directs the head into the acetabulum.

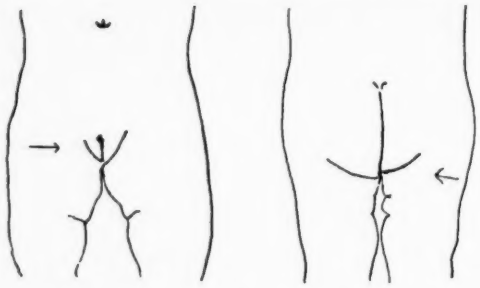

Fig. 3. The asymmetry of the inguinal and gluteal fold of right side is shown.

The infant wore the brace continuously and this necessitated the substitution of sponge baths for tub baths. Notwithstanding this handicap, and that this period included the warmest months of the year, the child developed rapidly and was in excellent physical condition. This shows beyond doubt that my treatment does not in any way retard the normal development of the child.

In this case I applied pressure very gradually over a period of months. I considered the comfort of the patient of greater importance than speedy reduction. The brace was applied on May 24, 1924. It was worn until February, 1925, a period of 8 months. On account of the rapid growth of the child, it was necessary on two occasions to remove the brace and substitute a plaster spica for a few days, while the brace was being lengthened. The X-ray pictures, taken at intervals of 2 weeks, showed a progressive approach of the upper end of the femur to the acetabulum and a gradual development of the upper rim of the socket, which was definitely apparent 4 weeks after the brace was applied. Toward the end of February the long brace was removed, and a short abduction splint, without the trochanter pad, was applied.

In this my first case, I was unnecessarily cautious in applying the pressure to the trochanter. It would have been perfectly feasible to bring the head into the socket within 4 weeks. Furthermore I left the brace on for several months longer than actually necessary. This child is now walking about without any limp or shortening, or any sign that there has ever been anything the matter with her. The X-rays, taken 4 years after the conclusion of the treatment, show two normal acetabula so completely alike that it is impossible to tell which hip had been dislocated.

Case 2. L. A., female, first and only child. Nothing abnormal was noted until she was 13 months old. After the child had been walking 1 month, the mother noticed a limp and she took her to the Hospital for the Ruptured and Crippled. There the diagnosis of congenital hip dislocation was made. Reduction under an anæsthetic and a plaster-of-Paris cast were advised. The parents did not agree to this. Within 2 weeks they took the child to a private physician, who also advised admission to the hospital, reduction of the dislocation, and the application of a plaster-of-Paris cast. After seeing the X-ray plates, however, he said he would treat the child in his office without an anæsthetic and without manipulation. A plaster-of-Paris spica was applied with the leg in slight abduction, and kept on for 8 weeks. Three more spicas were applied with the leg in various positions for a period of 6 months. Then a brace was applied. This was a Thomas knee splint with leg attachment. The brace was used for 6 months. During this whole year the child was allowed to walk. At the end of the year's treatment, the X-ray plate showed that the head was not in the socket, although with traction applied to the leg, the head could be brought down to the level of the acetabulum, but it was separated a goodly distance from it. The mother was then notified that an operation including bone transplantation should be performed. This procedure was declined.

The child then came under my care, when she was 2 years and 7 months old. I found the left hip still dislocated, as shown in the X-ray picture (Fig. 2). A brace was ordered and at Christmas in 1928 was satisfactorily fitted and applied. This brace was similar to the one used on my first case. The screw pressure was applied to the trochanter more rapidly than in the first case, and within 5 weeks the dislocated head was in the socket and has been there ever since. The patient was not allowed to walk during the entire time of the treatment. The brace was worn a little over 4 months.

I did not permit the child to walk for the following reasons: The frequent X-ray pictures showed that the socket was developing so well without weight bearing that I wished to challenge the theory, advanced by Lorenz and others, that functional weight bearing is necessary for deepening the acetabulum. To my mind the main requisite for deepening the acetabulum is the removal of the pressure of the head from the upper rim. The X-ray pictures all show how rapidly this rim develops as soon as the trochanter pad has pushed the head down into what is to become the socket. I also feel that when the head is surrounded by a well developed acetabulum, the traumatism of weight bearing will be less, and that no damage will come to the head in later years. This damage has been seen with persistent regularity in cases treated by the method now in general use, in which a soft cartilaginous head is supposed to pound out a hollow in the harder bony socket.

Case 2 has been very instructive. It shows that the trochanter pressure can be applied without inconvenience strongly enough to bring the head into the socket within 5 weeks. And this was

accomplished in a child 2 years and 7 months old. The development of the upper rim of the acetabulum in Case 2 progressed satisfactorily. You will see in Figure 2 how a curve is beginning to appear in what will be the roof of the socket. All of this shows that while the ideal time for treating these patients is the earliest months of life, the method has been found equally effective in an older child.

These two cases had single dislocations. I am anxiously awaiting the opportunity to test the method in cases with both hips dislocated, because we know that the prognosis in bilateral dislocations is not as good as in single dislocations. With my method I am confident that the treatment will be equally as successful in bilateral as in unilateral dislocations.

SUMMARY

It should be our duty to emphasize the fact that congenital hip dislocation can be diagnosed in the first 3 months after birth. This is important alike to the family doctor and the pediatrician.

The present method of handling these patients is unsatisfactory. Now, treatment is begun too late, for when treatment is delayed serious bony changes take place thus making reduction and retention difficult.

As to the closed method of treatment, this means of reduction must necessarily damage all the structures making up the hip joint. This damage is progressive and leads to further deformities and to disability in later life.

Regarding the surgical treatment, some authorities advocate and use the open operation in every case. Such treatment requires much time —sometimes 9 months to several years—and the result is uncertain. It requires repeated narcoses, the patient suffers much pain and inconvenience, and the method is not entirely free from danger to life.

The physiological treatment which I have just described is simple, is applied with little inconvenience to the patient, assures normal development of the femur in the acetabulum; furthermore, it requires much less time than the other methods—no more than 3 months—and if the treatment is properly carried out, should result in a high percentage of cures.

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FOUR RARE RECTAL TUMORS

INTRARECTAL SOLID TERATOMA, FIBROLEIOMYOMA, PARAFFINOMA, AND CHORDOBLASTOMA[1]

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THE purpose of this paper is to report four cases, unrelated except in that they are rectal lesions of rare occurrence and are interesting pathological types.

INTRARECTAL SOLID TERATOMA

Dermoid cysts and tumors are not uncommon, and the supposedly related teratomata are scarcely rare, but the particular tumor about to be described must be considered a most exceptional lesion. In an extended search, only three descriptions of similar tumors were found, and references, not accessible, to a few others were encountered. Whether these latter are actually identical cannot be stated without study of the original articles, not so far available to us.

CASE 1. Mrs. M. L. C., white, aged 35 years; complained of hair growing from anus. She has been forced to cut this off at intervals and this has been going on for the past 8 years. She was very constipated, had some discomfort in rectum if she sat for a long time, and had pain in lower spine. No mass protruded from the anus, and there was very little bleeding. On examination a strand of long, fine, straight dark brown hair was seen protruding from the anal orifice. The hair on the patient's scalp, pubis, and perineum was blond. On rectal palpation an ovoid mass, firm, movable, about the size of a large plum could be felt. This mass was fixed by a broad pedicle to the posterior rectal wall about 10 centimeters above the anal margin. With the proctoscope an ovoid white tumor could be seen just above the lowermost rectal valve, from which hair was growing. Operation was advised, and on April 3, 1928, was performed at the Union Memorial Hospital, under ether anæsthesia. The sphincter was widely dilated and the tumor mass exposed. The mass was about 5 centimeters in diameter. It was connected by a pedicle 4 centimeters long to the back of the rectum about the level of the third sacral vertebra. This pedicle passed directly through the rectal wall and was covered with white skin. The red mucous membrane of the rectum formed a sharp contrast to the white skin of the tumor pedicle. The rectal mucosa was divided from the pedicle on all sides and the pedicle was dissected backward behind the rectal wall as far as its attachment to the fibrous tissue in front of the sacrum. A clamp was put across the base at this point, the pedicle was divided, and the tumor was removed. The base of the pedicle was then transfixed with a suture above the clamp and tied off. The open cavity thus made in the posterior wall of the rectum was packed with dry gauze which was brought out through the anal orifice. The patient left the table in good condition and made an uneventful recovery. At the end of 3 weeks the wound made in the posterior rectal wall had completely healed, and the patient was discharged as cured. She was seen 8 months later and was entirely well.

Gross pathology. U. M. 2232, C. H. I. 9665. The tumor is comma shaped and smooth with small patches of delicate long brown hair growing on the under surface and sides. The head of the comma measures 5 by 3.5 by 4 centimeters, while the tail measures 4 by 1.2 centimeters. On section, the entire tumor is found to be surrounded by a well defined layer 2 millimeters thick which is radially striated. Beneath this, the tissue consists of mottled white bands interspersed with irregular lemon colored areas. Projecting above the surface at about its center is a pearly white, hard object 3 by 2 millimeters which looks very much like a tooth or piece of bone.

Microscopic examination. The tumor is surrounded with cornified squamous epithelium. The germinal layer dips deep down into the corium. The main body of the tumor is made up of bundles of smooth muscle and connective tissue, but there are also alveoli of fat, racemose sweat glands, bone, nerve fibers, and hair follicles.

The tumor removed is well presented in its anatomical relations, its size, gross appearance, and cut surface by the accompanying sketches, which also illustrate the steps of the operative removal (Figures 1, 2, 3, 4, 5, and 6). In short, this tumor is a teratoid mass of mixed tissues, but unlike an ordinary dermoid is not cystic, and instead of being a cavity lined with skin is a solid mass covered with it. Further, it did not lie before or behind the rectum, but swung free in the lumen of the bowel, attached by its pedicle to the posterior rectal wall. As has been said, dermoids and teratomatous tumors are not especially rare, and one of the regions where they are apt to occur is in the rectal environment, behind the bowel, near the coccyx, or in the rectovaginal septum. Such cysts in rare instances may rupture into the bowel.

Maingot and Saphir report such cases, in each the trauma of labor being the cause of the rupture. In Maingot's article the tumor passed per rectum was described as consisting of a mass with four distinct cysts, not communicating, and containing caseous material, hair, unstriped muscle, epithelium, cartilage, and fibrous tissue. A lacerated surface on the anterior rectal wall was thought to be the point of attachment of the tumor. Saphir's patient discharged a mass of hair and sebaceous material per rectum during labor, and later a rent was seen in the anterior rectal wall which opened into a cyst cavity lined with a hair growing wall. Saphir refers to several other similar reports in the literature.

[1] We have been aided in the preparation of this work by a grant from the Hartley Foundation.

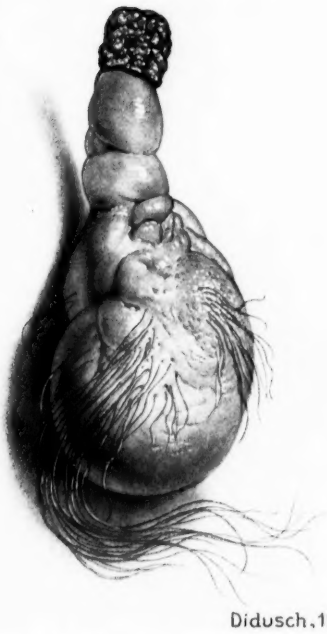


Fig. 1. Excised teratoma of rectum.

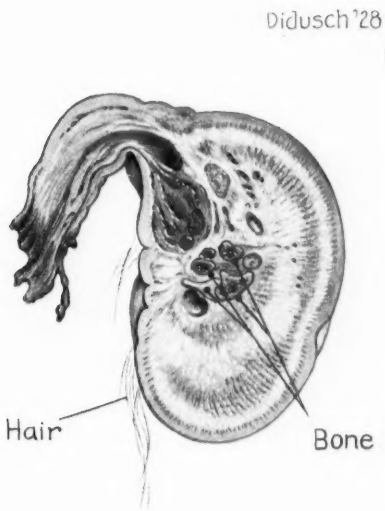


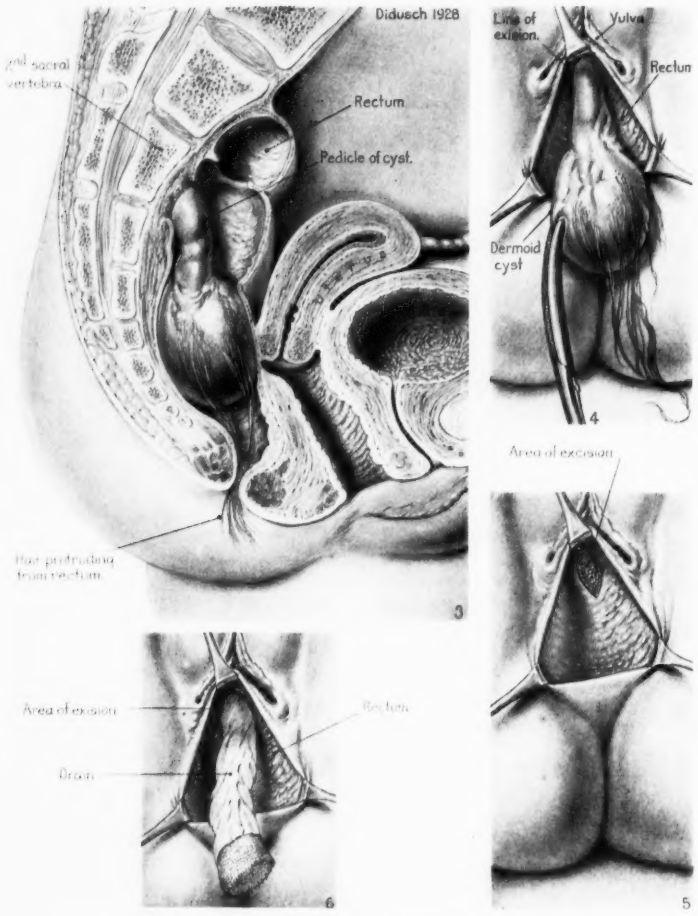
Fig. 2. Teratoma, cut surface.

Danzel, Port, and Bensaude and Rachet each report one case very similar to the one herewith recorded. All of the patients were women. Their ages were 16, 25, and 39 years respectively. In each instance hair growing from the anus was the symptom that attracted attention. Danzel operated on his case and removed a tumor 4.5 by 4 by 3.5 centimeters, which contained a tooth, much hair, bone, fat, and rudimentary brain tissue. The patient died over 3 months later from a slow perforation through the anterior rectal wall where the tumor had been attached.

Port's patient finally extruded the tumor per anum, and its pedicle was then ligated and the mass removed. It was a mass 2.5 by 2 by 1.5 inches, covered with ordinary skin, growing hair, and containing fat, bone, a tooth, and muscle fibers.

Bensaude and Rachet did not remove the mass, but saw it through a proctoscope, and described it as a mass the size of a cherry, of a pinkish white color, growing hair from its surface, and attached to the anterior rectal wall 13 centimeters above anus. These writers refer to a thesis by Salmonoff (Berlin, 1902), who reports eight dermoid cysts above the anus, two of which had produced hair protruding through the anus. Neither of these was operated on as the symptoms did not seem to warrant it. They also quote Longuet, who in 1898 reported 3 cases, but no details are given.

There are a few comments to be made on this assembly of cases. All are in women and all in the earlier half of life. In all, the symptom complained of was hair protruding from the anus. In several, there was some difficulty in defæcation. No bleeding is reported in any case. Saphir's case of ruptured cyst suggests a possible explanation of the evolution of the form of tumor here considered: a tumor or cyst lying close under the rectal mucosa, which ruptured into the lumen would, if it continued to grow, perhaps protrude into the bowel as a skin covered, hair growing mass. In other words, a dermoid or teratomatous cyst which ruptured into the bowel might, by continued growth, turn inside out and its hairy skin lining would then become its covering. As to treatment, although surgical removal may at times seem a formidable problem, no other method offers a satisfactory solution. If the patient suffers little except the annoyance of the protruding hair, and the tumor is so situated as to render operation exceptionally difficult or dangerous, good judgment would naturally lead one



Figs. 3, 4, 5, and 6. Teratoma of rectum.

to defer interference until it should become more clearly indicated.

FIBROLEIOMYOMA OF RECTUM

Fibrous tags about the anus, resulting from organized thrombosed hæmorrhoids or enlarged and fibrous skin folds are, of course, exceedingly common. Polypi in the anal canal and rectal lumen of small or moderate size, with a fibrous stroma and epithelial covering, are often seen. On the other hand, true rectal tumors of distinctly neoplastic character as distinguished from chronic inflammatory or hyperplastic masses of tissue, that consist of smooth muscle or fibrous tissue or a mixture of both, are very rare indeed. Thus Ashton, in 1865, quotes only one case, a fibrous tumor weighing one-half a pound, growing from the anal margin. Tuttle says that true fibromata of the rectum are exceedingly rare and refers to two cases in the literature, neither of them his own. Ball mentions fibromyoma as being a very rare rectal growth and reports one case. Gant "does not remember encountering a typical myoma of the anal region," but states that fibromyoma are occasionally met with in the rectum or recto-vaginal septum. Hill reports seeing only one case of myoma. Lynch reports records in the literature of 80 cases of myoma of the entire intestinal tract, of which number 20 per cent, or 16 cases, occurred in the rectum or

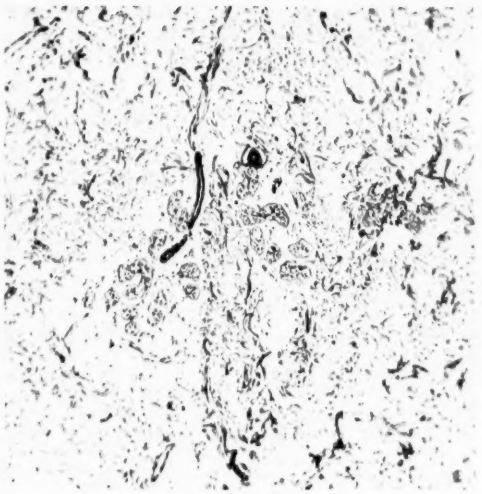


Fig. 7. High power photomicrograph of rectal teratoma showing sweat glands and cross section of hair.

anal region. These are all references from textbooks written by specialists in the field of rectal surgery; men of wide personal experience and familiarity with the literature. Hunt, in a special study of such cases published in 1921, reports 4 cases of his own, 2 of pure myoma and 2 of fibromyoma. In an extensive review of the literature he could find only 20 cases reported since 1872 that he accepts as myoma or fibromyoma. From his own cases and those collected, he summarizes the few following data: 13 patients were women, 10 were men, and in 1 instance the sex was not recorded. The age incidence ran from 21 to 85 years. Malignancy developed in one case. He gives brief abstracts of all the cases from the literature and adds the record of his own 4 cases. Wolfer, in an article on leiomyomata of the intestinal tract, points out that rectal myomata may protrude into the bowel like polypi or grow outward from it, usually behind toward the hollow of the sacrum. He refers to such a case, reported by Senn, which weighed 12 pounds.

It will be seen from the survey of the subject that we are dealing with a very unusual tumor of the anorectal region. Such tumors need to be borne in mind because of the possibilities they present for mistakes in diagnosis. Our case had been misdiagnosed before coming into our hands, and our own recognition of its exact nature awaited the operative and histological findings. As seen by reference to the reported cases, the most common error is to mistake these essentially benign tumors for malignant disease, with the danger of being led into an extensive destructive operation unnecessarily.

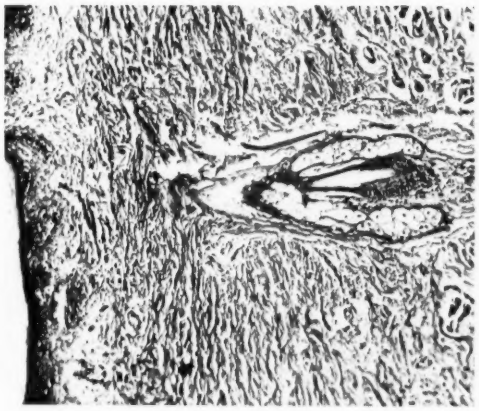


Fig. 8. High power photomicrograph of rectal teratoma showing root of hair follicle and surface epithelium.

The report of our case follows:

CASE 2. Mrs. I. V. C., aged 74 years, had complained, at intervals for several years, of rectal trouble. For the past 2 months this has been more acute. There has been a good deal of pain in the anal region and difficulty in securing bowel movement, feeling of pressure, and occasionally

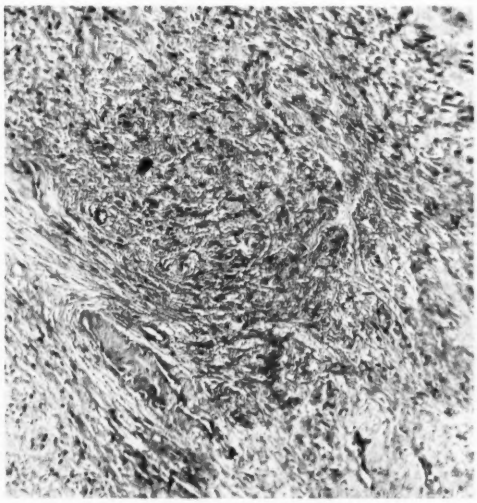


Fig. 9. High power photomicrograph of rectal fibroleiomyoma showing bundles of smooth muscle and fibrous tissue.

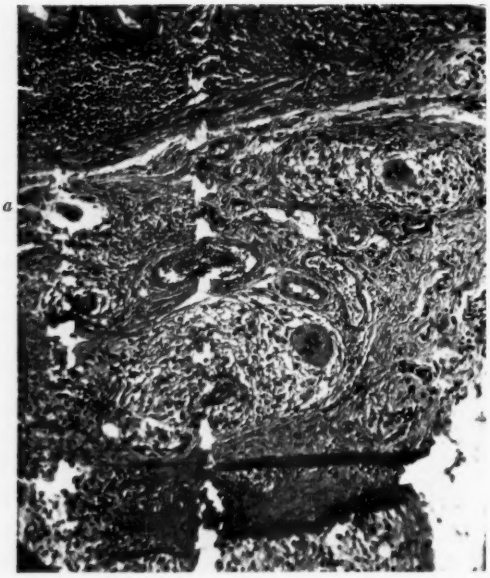


Fig. 10. High power photomicrograph of rectal paraffinoma showing intact mucosa, pseudo tubercles with giant cells and rarefied tissue about them. At *a* there is a small hyaline area interpreted as paraffin.

the passage of some blood or mucus. There has also been some aching in the back and down the legs. Six weeks ago she consulted another physician who found a swelling back of the anus which was taken to be an abscess, and this was incised. The wound did not heal properly, although no pus was found at the time of incision. The mass still persisted as before. On examination there was found an incision in the posterior midline just behind the anus, with curious looking base and punched out edges. The base was firm, rather gelatinous-looking with a tendency to bulge upward into the wound. Preliminary diagnosis was possible colloid carcinoma. A few small hæmorrhoids were also present.

Operation was advised, and on November 19, 1927, was performed at the Church Home and Infirmary, ethylene gas anæsthesia being used. The wound already existing was enlarged and a large tumor was found underlying it. This tumor was completely and firmly encapsulated and it shelled out of its capsule very readily with very little bleeding. It formed an ovoid mass 6 centimeters long by 4 centimeters wide. There was a good sized cavity left by its removal, which was partially closed by bringing the sphincter and levator muscles together from the two sides with interrupted catgut sutures. The remainder of the wound was packed with iodoform gauze. A naked-eye inspection of the cut surface of the tumor led to a diagnosis of fibroma as is shown in the pathological report which is given below. The wound healed very quickly and very cleanly.

The patient's constipation was greatly improved following operation, and the pain in the back and down the legs disappeared. Patient was seen about a year after operation and there was no evidence of recurrence.

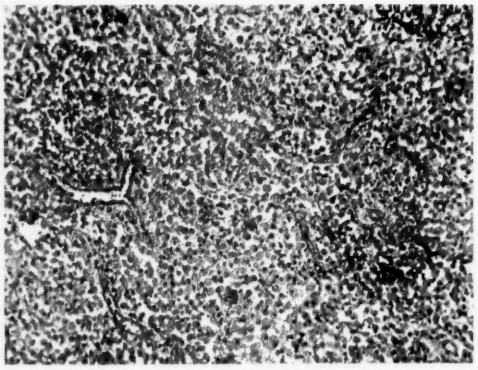


Fig. 11. High power photomicrograph of chordoblastoma showing large polygonal cells arranged in strands with occasional syncytial masses and foam cells.

Gross pathology. Section No. 8409. The specimen consists of a hard, oval, encapsulated mass measuring 6 by 4 centimeters. The mucous membrane is ulcerated down to the muscularis. Its base is smooth and clean. Section through the mass shows a thick capsule surrounding it. The tissue is a uniform grayish pink with the fibers arranged in whorls.

Microscopic examination. On examination under the low power, the section has the appearance of a fibromyoma of the uterus. There are strands of hyalinized connective tissue interspersed with whorls of smooth muscle fibers cut at various angles. Large venous sinuses are present, and there are occasional smaller arteries with thick hyaline walls.

PARAFFINOMA OF RECTUM

No record of any case like this one has been found in a fairly extensive search of the literature. Paraffinoma, of course, is a lesion of definite etiology, and the history of this patient makes it quite evident that the treatment he must have received for hæmorrhoids consisted of the injection of paraffin into the rectal wall. The history of the patient follows:

CASE 3. Mr. R. Z. D., aged 61 years. Patient used to be troubled with hæmorrhoids which protruded but did not bleed much. In May, 1926, he had these hæmorrhoids treated by an injection method. The patient does not know what the material injected was. Following the injection, there persisted some tenderness and swelling. The complaint at the present time is persistent and increasing constipation, which has become very pronounced during the last 2 or 3 months. There has been no rectal bleeding, no pain, and no definite tenesmus. No nausea, vomiting, or abdominal cramps, and no loss of weight. There have been no bladder disturbances of any kind. The principal and only complaint is extreme and increasing constipation. On examination, nothing was made out in the abdomen. Rectal inspection was also negative. Rectal palpation, however, showed an annular constriction just above the anal canal about at the level of the apex of the prostate gland. This constriction was quite hard, fixed, with well defined edges and a smooth surface. With the proctoscope the lumen of the bowel was seen to

be reduced at the level of the stricture to about one half of its normal diameter. The mucous membrane at this point looked normal, and no ulcerations were seen. Diagnosis was rectal stricture due to a tumor-like mass of annular form, not involving the mucous membrane. A preliminary diagnosis of sarcoma of the bowel wall was made, but as this was by no means a strongly held opinion, it was decided on March 15, 1928, to remove a specimen for microscopic study. The report from this small piece of tissue was "tuberculosis of the rectal wall." As the lesion was strictly localized, the patient was advised to have an operation done for the removal of the diseased area.

Operation was performed at the Church Home and Infirmary, March 17, 1928, ethylene gas anæsthesia being used. A circular incision was made at the anal margin and prolonged backward in a straight line toward the coccyx. The coccyx, however, was not removed. The sphincter muscle was carefully dissected away from lower portion of the bowel and preserved in place without being divided. The bowel, including the mass in its wall, was then dissected loose from the surrounding structures up as high as the peritoneal cavity, which was not opened. The whole rectum was thus mobilized. The bowel was then drawn through the sphincter and the distal portion amputated, a margin of about 1 inch being allowed above the area involved in the disease. The proximal stump of the rectum was then sutured into the anal skin as in a Whitehead operation. The patient left the table in good condition. His wound healed quite well, although it was several weeks before he regained control of his sphincter muscle. At the present time his control is practically perfect. The microscopic examination of this tissue showed very interesting further development.

Gross pathology. The specimen is that of the lower portion of the rectum extending 7.5 centimeters from the anal margin. When the lumen was opened the mucous membrane appeared intact. Beneath the mucosa extending into the submucosa and muscularis, is a hard circular cuff which on section consisted of gray fibrous tissue in which were hard, clear, transparent, gelatinous, and yellow fatty areas. Two glands, about 2 millimeters in diameter, removed from the external surface of the rectum, were also present. These showed no abnormality in the gross.

Microscopic pathology. The mucosa over the entire section was intact. Just beneath this, the tissue was heavily infiltrated with small round cells, and from here down through the muscular coats were structures which at first glance gave the impression of tubercles. The tissue in these places seemed rarefied. The cells are stellate with fine fibrils connecting each with the other. Giant cells are present in large numbers, some of them within the pseudo-tubercles and others loose in the muscle with practically no cellular reaction about them. They are characterized by having their nuclei grouped at their centers. Nowhere is there any evidence of caseation, and there is usually no round cell reaction about the tubercle-like structures. Dr. James Ewing saw the section and makes the following comment: "The section of rectal tissue which you sent me looks like a paraffin tubercle. I think the patient must have had an injection of paraffin which produced this chronic progressive, productive inflammation. There are a few hyaline areas which were found after long search, which we are willing to call droplets of paraffin."

The point of paramount interest here, aside from the unusual employment of paraffin injections in the treatment of hæmorrhoids, was the difficulty of diagnosis. It must be remembered that no statement was obtained as to the material that had been used for injections and that a considerable time had elapsed since the injections had been given. The case presented certain features suggesting that the easily felt stricture was a malignant growth. The annular mass was very hard and inelastic and fairly fixed to surrounding structures. On the other hand, it lacked the ulcerated nodular surface that a carcinoma of this size would be expected to present. The smooth intact mucosa over the mass did not suggest a tuberculous process either, and the preliminary diagnosis was sarcoma of the deeper structures of the rectal wall, without invasion of the mucosa. It was because of the unsatisfactory nature of this diagnosis that a biopsy was done before attacking the lesion surgically. The biopsy report of tubercle eliminated the question of malignancy and settled the type of operative procedure in favor of local resection rather than radical excision of the rectum. When the whole specimen was examined it was clear that the tubercle formation was of the foreign body variety and not due to infection with the Koch bacillus.

SACROCOCCYGEAL CHORDOBLASTOMA

Within the past few years the subject of tumors developing from the notochord has received a good deal of attention, as is evidenced by the carefully prepared case reports and reviews of the literature. In this paper we make no attempt to review the literature, as those who are interested may refer to the publications of Albert, Capell, Stewart, Hutton and Young, Ramsey, and others. We wish simply to report a case of this unusual condition.

As is well known, these tumors occur at any point along the spine, but are most frequently found at the spheno-occipital synchrondroses and more rarely at the sacrococcygeal junction. They develop from cell rests, remnants of the chordo dorsalis which are found in about 2 per cent of human embryos in the intervertebral discs.

The first case of chordoma was described by Lushka (1857). In this year Virchow also described these tumors under the name of "Ecchondrosis Physaliphora," believing them to be cartilage which had undergone hydropic change. Mueller, however, first described the true nature of these growths. He called attention to the notochordal remnants in the intervertebral discs and suggested that these tumors developed from them. It remained for Ribbert (1894) to give the name "chordoma" to these growths and offer experimental proof of their origin.

In the case about to be reported, the cause of the patient's illness was not diagnosed for nearly 9 years, during which time he was treated for fistula-in-ano, perirectal abscess, and recurrence of these conditions. The true nature of the condition was discovered when the tract was laid wide open and pieces of the gelatinous tissue which lined it were subjected to microscopic examination.

CASE 4. Mr. A. L. S., aged 27 years, was first seen by one of us January 17, 1928. His complaint was "rectal trouble," which had begun about 9 years ago. He first noticed a swelling near the anus which later was operated on February 9, 1925, and was considered a perirectal abscess. Several months later he was operated on for "condylomatous tags." He contined to have discharging sinuses, and a few days before being seen by us another abscess opened externally on the right buttock. This was still draining at the time of the examination. He complained also of frequent inclination to defæcate without being able to empty the bowel completely and had the sensation as if there were a lump near the anal margin. There had been no discharge of blood from the rectum, but mucus and pus were frequently passed. He had lost about 18 pounds in weight during his entire illness.

The patient's general physical examination was quite normal, except for a moderate anæmia and a leucocytosis of 12,500. X-ray examination of the chest and long bones and pelvis showed no metastases. On rectal examination, the sphincter control was found somewhat weak. A discharging sinus was found in the right buttock. A probe passed inward toward the anal canal but did not enter it. There were several granular looking skin tags about the anus. On digital examination, there was felt a great deal of scarring about the lower rectal wall, with bands and irregular nodules. Diagnosis of some unusual type of fistula was made; possibly due to tumor.

Operation, Church Home and Infirmary, January 19, 1928, ethylene gas anæsthesia. The external opening on the right buttock was injected with a solution of methylene blue. This immediately came out of the anal canal in large quantities, showing a complete fistula. The tract was divided on a grooved director and found to lead upward into the rectum to a point about 1.5 centimeters above the skin margin in the posterior midline. There were two or three lateral sinuses branching off from the main tract, which burrowed upward a long distance into the pelvic fat. The entire fistula was lined with thick, coarse granulation tissue and gelatinous material. It was laid wide open throughout its entire extent and thoroughly curetted. In order to do this, it was necessary to divide part of the sphincter muscle in the posterior midline. Bleeding points were tied and the wound packed with five strips of iodoform gauze. The patient left the table in good condition. The fistula was an exceptionally deep and tortuous one and will probably take a long time to heal.

Postoperative history. For about 2 weeks following the operation, the patient experienced considerable pain. The wound discharged copiously for about the same period. Gradually the pain and discharge diminished, the size of the wound reduced, and the patient's general condition improved. He was given radium treatment to supplement the obviously incomplete surgical removal of the disease. His sphincter control became better, and he was discharged from the hospital in fairly satisfactory condition. When last heard from, over a year after operation, his wound had completely healed, he had gained weight, was working as usual, and complained of nothing except some weakness of sphincter control.

Gross pathology. The tissue consists of several pieces of tissue varying in size from 3 centimeters to small scrapings. It showed small and large lobulated gelatinous translucent areas interspersed with bands of opaque connective tissue. Several hæmorrhagic areas of various sizes are present in different regions.

Microscopic examination. The thick fibrous capsule so uniformly described about these tumors is absent because the tissue received was from curettings rather than an enucleation of the growth. There are, however, strands of fibrous tissue throughout the growth, tending to divide it into pseudo alveoli. The cells are large, oval to polygonal in shape, with deep staining round and oval nuclei. Some of the syncytial masses contain several nuclei. The cytoplasm is pale staining and granular. Some of the cells are ballooned with masses of blue staining mucin, the so called "physaliphore cells" and others are vacuolated, breaking up to form the characteristic "foam cells." The cells are arranged in solid masses or in irregular strands, thus giving the appearance of liver tissue, the interstitial tissue being filled with vacuoles or mucin. Throughout the tumor, and especially along the strands of connective tissue, is a marked round cell infiltration.

Photomicrographs of tissue from each of these four rare tumors are presented.

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THE USE OF INTRAVENOUS GLUCOSE IN DIABETIC PATIENTS

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IT is well known that in surgical cases the use of intravenous glucose following operation, and glucose or carbohydrate in some form the night preceding the operation, is a very valuable measure. This applies especially to cases in which the patient starts vomiting after the operation and can hold nothing on his stomach, not even water, and through incessant vomiting, becomes partly dehydrated, developing a degree of alkalosis which in turn aggravates the vomiting, thus establishing a vicious circle. As the result of the administration of intravenous glucose solution, this vicious circle is broken, and the patient has an infinitely better chance of recovery.

While in the case of non-diabetic patients, there is no doubt as to the value of the intravenous administration of glucose, in the case of diabetic patients, the following questions arise: "Can we safely give glucose to diabetic patients? Will we get the same result as in the non-diabetic cases?"

While a normal individual apparently has available an unlimited supply of endogenous insulin, so that no matter how much carbohydrate he is given he can take care of it, the diabetic patient, on the other hand, has not enough endogenous insulin available. If the use of glucose in the case of a non-diabetic individual is a good physiological measure, it should be equally good in the case of a diabetic individual if in some way we can assist the patient to take care of the added glucose in the blood stream. In the pre-insulin era this was impossible, for any addition of glucose to the already increased sugar in the blood would have been an unsafe procedure. However, now that insulin is available and may be used as frequently as the need for it is indicated, the problem has taken on an entirely different aspect. We can supply the needed insulin to the body from without, and thus the diabetic individual may have the advantage of this, and the mortality of operations on diabetic patients may be lowered.

The method which I have used here in the Clinic has been the intravenous administration of 250 cubic centimeters of a 10 per cent solution of

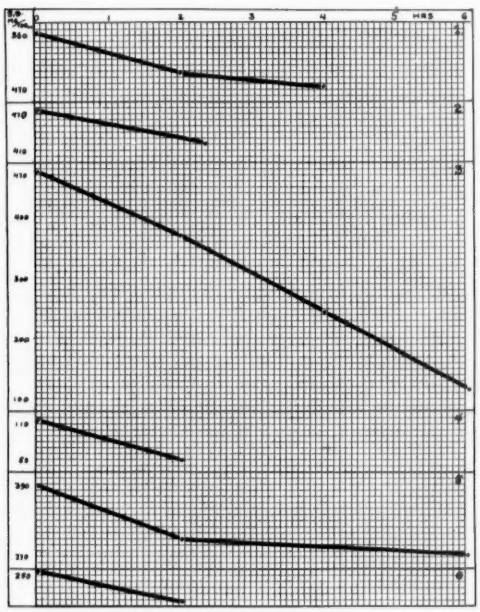
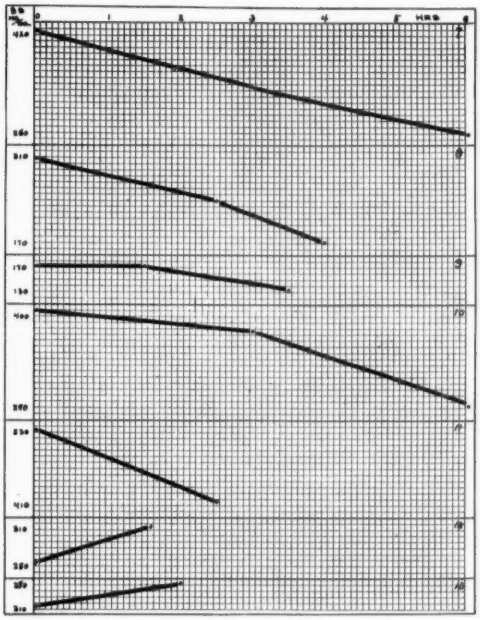


Chart 1.



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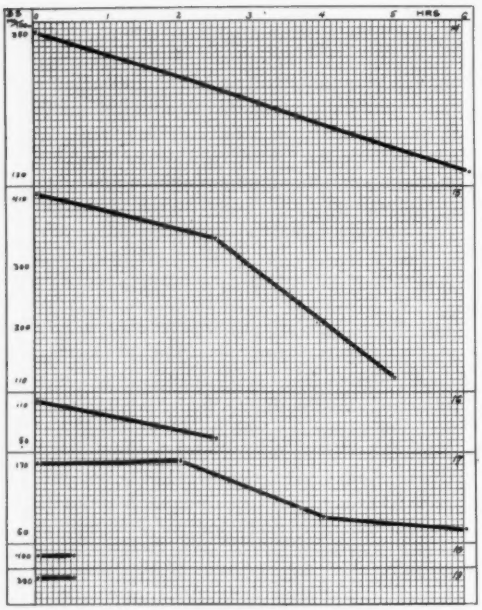

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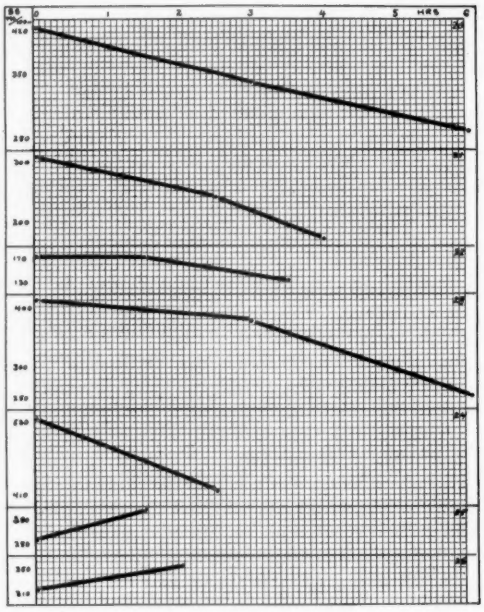

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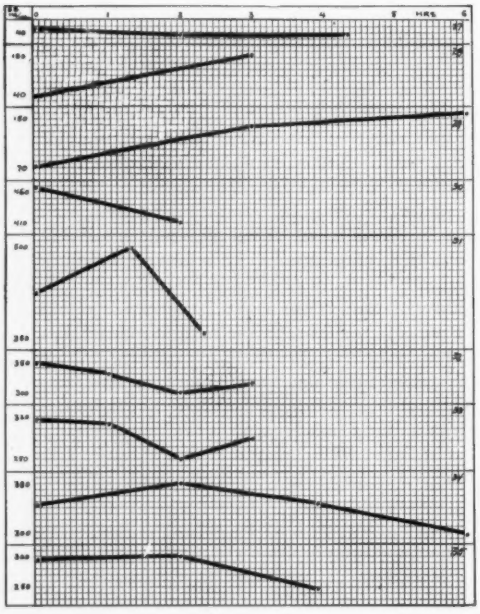

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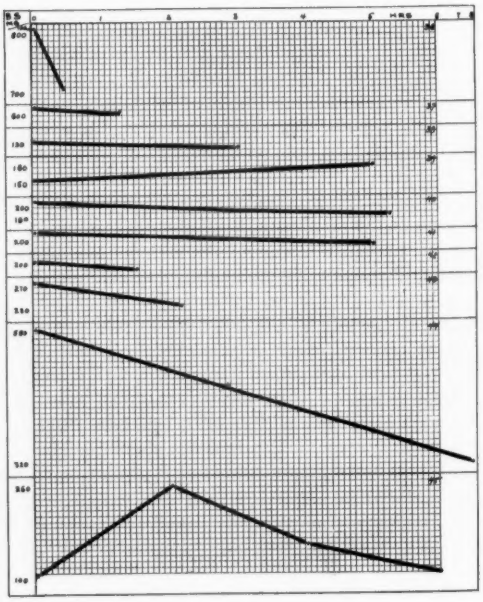

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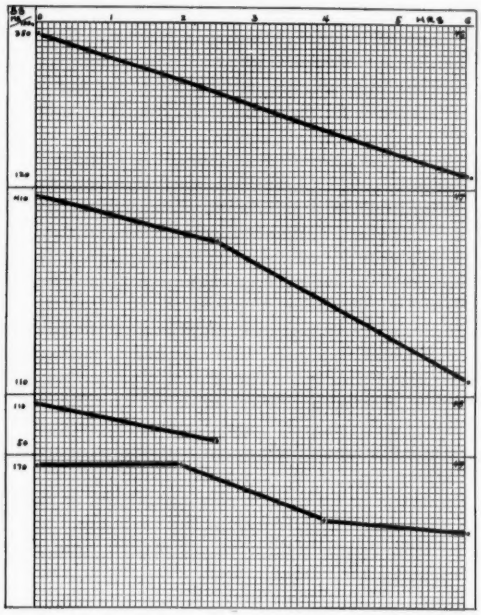

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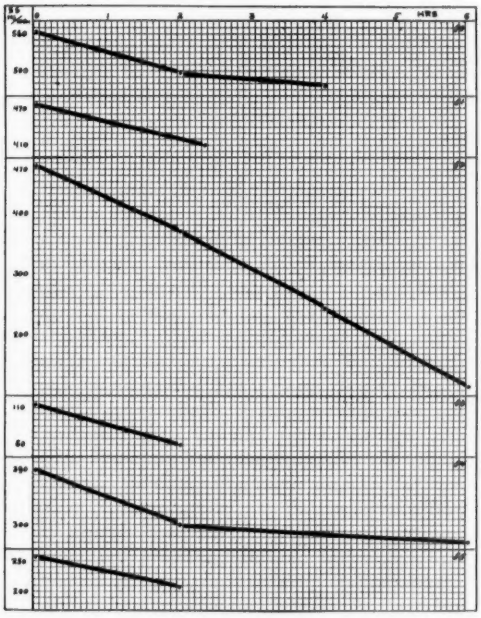

Chart 8.

TABLE I.—CHANGES IN BLOOD SUGAR AFTER THE INTRAVENOUS ADMINISTRATION OF GLUCOSE—FIFTY-FOUR CASES

Case	Changes in blood sugar mgm. per hr. Fall	No change	Rise
1	22	..	....
2	24	..	....
3	60	..	....
4	33	..	....
5	19	..	....
6	38	..	....
7	28	..	....
8	34	..	....
9	10	..	....
10	26	..	....
11	47	..	....
12	.....	..	38
13	.....	..	18
14	39	..	....
15	58	..	....
16	24	..	....
17	18	..	....
18	.....	0	....
19	.....	0	....
20	28	..	....
21	34	..	....
22	10	..	....
23	26	..	....
24	47	..	....
25	.....	..	38
26	.....	..	20
27	1.8	..	....
28	.....	..	22
29	.....	..	14
30	28	..	....
31	25	..	....
32	11	..	....
33	10	..	....
34	8	..	....
35	14	..	....
36	208	..	....
37	6	..	....
38	3	..	....
39	.....	..	5
40	4	..	....
41	4	..	....
42	9	..	....
43	18	..	....
44	22	..	....
45	.....	..	0.3
46	38	..	....
47	50	..	....
48	24	..	....
49	16	..	....
50	22	..	....
51	28	..	....
52	61	..	....
53	33	..	....
54	19	..	....
54	1287.8	0	155.3

Of a total of 54 cases, 44, or 81.5 per cent, showed a fall of blood sugar; 2, or 3.7 per cent, showed no change; and 8, or 14.8 per cent, showed a rise of blood sugar. The average fall of blood sugar (44 cases, or 81.5 per cent) was 29 milligrams per hour; the average rise of blood sugar (8 cases, or 14.8 per cent) was 19 milligrams per hour.

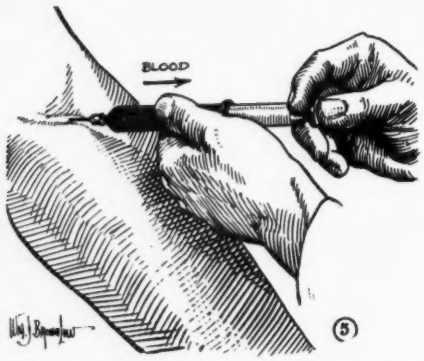

Fig. 1. Withdrawal of specimen of blood before administration of glucose.

glucose to which from 20 to 50 units of insulin has been added, the amount of insulin depending on the severity of the diabetes and the height of blood sugar at the time. This procedure can be repeated two or even three times a day, as the need for it is indicated.

When glucose is given intravenously in the case of a diabetic patient, the glucose apparatus should be filled to the tip with the warm solution. Cooling should be allowed for during the process, so that the solution in the bottle should be quite warm. A specimen of blood should then be secured through a venepuncture, for blood sugar determination (Fig. 1). While the needle is still in the vein, the end of the needle next to the syringe should be grasped with a hæmostat so as not to dislodge the needle from the vein. The syringe

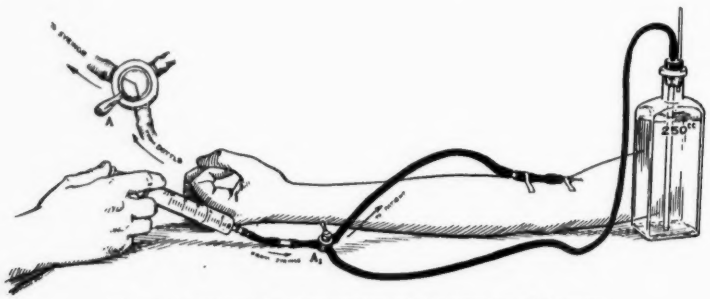

Fig. 2. Apparatus for intravenous administration of glucose.

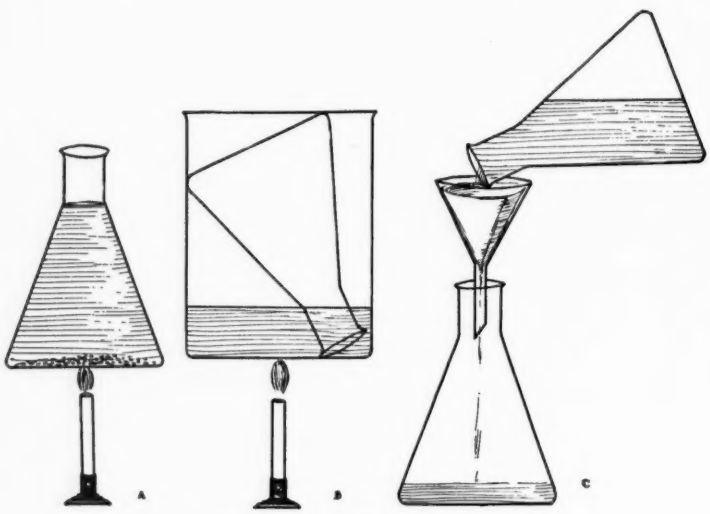

Fig. 3. Method of sterilizing glucose solution and container.

filled with blood is then disconnected from the needle, and the adapter of the glucose outfit inserted into the needle in the vein. In this manner blood is secured and glucose administered through one venepuncture. A practical outfit for the intravenous administration of glucose is illustrated in Figure 2. This consists of an ordinary bottle with a capacity of 250 cubic centimeters (8 ounces), rubber tubing, a three-way stopcock, and a 10 cubic centimeter Luer glass syringe. By one turn of the stopcock the syringe is filled, by another turn of the stopcock its contents is emptied into the blood stream, and this procedure is repeated until all the solution is used up.

The preparation of the glucose solution is simple. Twenty-five grams (1 ounce) of chemically pure glucose is dissolved in an Erlenmeyer flask in enough freshly distilled water to make 250 cubic centimeters. This solution is brought to the boiling point (Fig. 3, A). The neck of another Erlenmeyer flask is sterilized in a beaker of water (Fig. 3, B) and the dissolved glucose is filtered from flask *A* to flask *B* (Fig. 3, C), the contents of which is simply brought to the boiling point, when the solution will be sterile and ready for use.

It may be difficult to make the venepuncture. Thus if the needle is quite sharp, as it should be, it may perforate both walls of the vein. Figure 4 illustrates such a mishap and offers a remedy. Simply pull slowly on the syringe and plunger at the same time, and as soon as the needle has entered the vein, blood will appear in the syringe.

When insulin is added to the glucose, the diabetic patient should theoretically be protected from a rise of blood sugar. That this is actually true in practically all instances can be gleaned from Charts 1 to 8, in which I have drawn the blood sugar curves following the intravenous administration of glucose plus insulin in a series of 54 cases of diabetes. These demonstrate clearly that there need be no fear of endangering the status of a diabetic patient by the administration of glucose if the blood sugar is checked by subsequent examinations. Even though the blood sugar should rise, this can be easily controlled by the administration of additional insulin either hypodermically or intravenously.

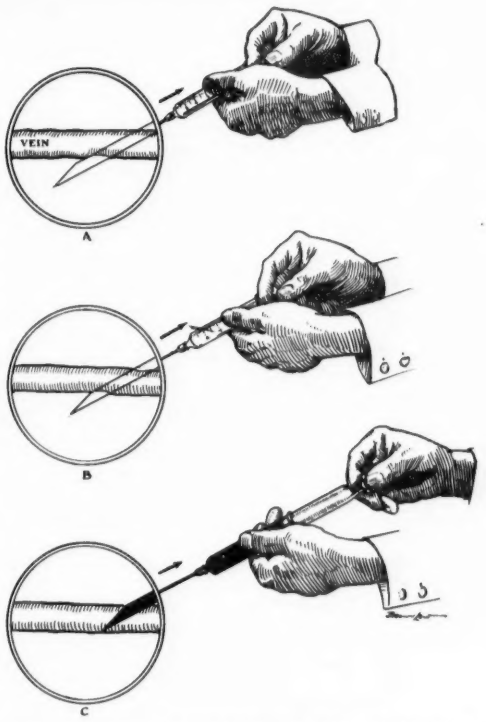

Fig. 4. A remedy in case both walls of the vein have been penetrated through venepuncture.

This series of charts has been drawn from data secured in cases of diabetes in which an operation has been performed, and in cases of diabetic coma in which also the use of intravenous glucose is a great aid in overcoming the acidosis and increasing the excretion of acetone bodies through the urine. Furthermore, the practically glycogen-free liver as well as the heart muscle is thus restocked with glycogen.

In Table I, the data illustrated by the charts are summarized. From these data, I believe that we can feel quite free, in cases of diabetes whenever this is indicated to use glucose intravenously to the great advantage of the patient.

EDITORIALS

SURGERY, GYNECOLOGY AND OBSTETRICS

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APRIL, 1930

THREE SCORE AND TEN

THE brain of man is a visual brain. The mind of man was built up coincidentally with the eye, and it is this fact, not the mechanics of the eye, that has made intellectual progress possible. In the lower vertebrates an expanded olfactory ganglion was the forerunner of the cerebrum, and the sense of smell not only controlled their behavior, but it remains, in the lower animals, the only special sense which is not relayed through intermediate ganglions. The great expansion of the cerebrum in man, however, completely overthrew the dominance of the olfactory sense, giving control to vision, and establishing direct relationship with consciousness, thereby governing behavior.

The microscope, introduced by the Janssen brothers, in 1590, was the most significant scientific contribution of all time and was destined to change the history of mankind, because it extended vision into the more minute, and thus made possible comprehension of the vast realm of micro-organisms.

My professional advent was early in the development of Pasteur's germ theory of disease and Lister's application of it to surgery. As a result of that epochal work through which came the elimination of contagious and infectious diseases, the average lifetime of man has increased 20 years. But we have not been so successful as had been expected in carrying the individual from middle age to the Biblical age of three score and ten.

Why is it, that whereas the total number of persons who reach middle life has been enormously increased, the relative percentage of those who reach three score and ten has not been correspondingly increased? There is no known normal length of human life. In the problem of life expectancy there are many factors to be considered of which heredity is the most important. Exposure to disease producing influences, the character of employment of profession, and hazards of all sorts, all must be taken into account in attempting to establish an age probability.

We commonly think of hazards in nature as being physical, but the emotional hazard must be taken into consideration as well. Generally speaking, the medical profession is rated high for longevity, but this is more true of the internist than of the surgeon. The statistics of the Royal Victoria Hospital, of Manchester, England, showed that the death rate among surgeons after 50 years of age was more than three times that among physicians in the same age period.

However, experience has shown that in the fifth decade, especially, if vitality is lowered for any reason, life may terminate as a result of a relatively unimportant affection, such as a cardiorenal disturbance or a pulmonary disorder. We must now undertake to determine

the nature of those obscure metabolic changes which lie behind these too early fatalities.

The investigations which are necessary to analyze the individual in his life processes lie in the colloidal field, beyond the microscope. With the microscope, particles 1/10 micron, approximately 1/250,000 inch, in diameter are visible, but the colloidal field includes particles between 1/10 micron and 1/1,000 micron, approximately 1/25,000,000 inch, in diameter. In this field, not the object itself but its shadow is seen, because the colloidal particle is larger than a ray of light and it reflects the light as though it were a mirror.

Below the colloidal field, in the division of size, lies the molecular field, and beyond that the atomic field. Because the atom is larger than the electromagnetic manifestation of the X-ray, it has been separated into the electron and the proton, which lie in the experimental field.

Although the single colloid particle or molecule cannot be seen with the eye, because it is so minute, colloidal particles or molecules may become visible in the mass aided by staining properties.

Geraghty and Rowntree took advantage of this fact in the development of the phenolsulphonephthalein test of the function of the kidney, which not only had the greatest scientific value in demonstrating the permeability of the kidney to certain substances with a urea-like filterability, but by timing the process of elimination gave an extraordinarily correct estimation of the function of the kidney. Rowntree and his associates in later experimentation with phenoltetrachlorphthalein demonstrated that the drug was always eliminated in the bile and perfected the best test known for function of the liver when jaundice is not present. And again, phenoltetrachlorphthalein was used as the starting point in cholecystography, in that it was shown that bile containing this dye was more opaque than normal bile. This research led to the recognition of similar opaque substances of even more valuable aid in eliciting diagnostic evidence of disease of the biliary tract through the X-ray.

We have become so "eye-minded" that it is difficult for us to appreciate that invisible colloidal and molecular particles are just as physical as though we could see them. After all, it is merely a question of size.

As surgeons we are interested in the metabolic processes in the preparation of elderly patients for operation. The advances made by biochemistry in securing better results in surgery, through rehabilitation of the patient, have had an equally profound influence in medicine and point the way to prolongation of life. W. J. Mayo.

LUMINAL AND THE NEWER CONCEPT OF ANÆSTHESIA

THAT there is dissatisfaction with our present anæsthetics, as commonly employed, is shown by the number of new methods of inducing anæsthesia put forward in recent years both here and abroad. The most significant feature of the viewpoint prompting this movement is its indication of a changing conception of the function of an anæsthetic. One has now a right to expect that an anæsthetic shall do more than abolish pain during operation and give the necessary relaxation with the minimum risk. From an increasing regard for the needs of a surgical patient as an individual and not as a lesion or a disordered mechanism, there comes a sense of how greatly the patient's burden could be lifted if he could be promised that he would know nothing of what takes place from the time of going to sleep on the night before operation until the day following

operation. An ideal anæsthetic would provide such an *oblivion* without complicating induction or adding to the risk and morbidity.

With this in mind, we have studied, during the last 9 years in over 1,100 selected cases, the two most widely known of the barbituric-acid compounds, *veronal* and *luminal*. In agreement with experimental and clinical work of other recent investigators, we believe that by a combination of anæsthetic agents one can stay within the limits of safety of each and exploit the good properties of several. We do not attempt to produce full surgical anæsthesia, therefore, with luminal (our preferred drug), but use it in doses sufficient to produce a narcosis, a "semi-anæsthesia." We prefer luminal because (1) there is a voluminous clinical and experimental literature, without a single authenticated death from the use of luminal alone (though single doses of 50 grains have been reported twice); (2) it causes less nausea and loss of equilibrium than does veronal; (3) veronal has a bad reputation, however undeservedly, as a suicidal agent, especially among the laity. The final surgical anæsthesia is induced by nitrous oxide or ethylene (in much lower concentrations than can be used otherwise), and is therefore *instantly controllable*, or by local or spinal anæsthetic.

We have learned to anticipate the desired "luminal effect."

Three hours before operation the patient is given the drug in one dose and it takes effect in about 1 hour. He comes to the operating room without interest in his surroundings, often asleep, but can be roused to answer questions. The first needle-prick of local infiltration or the first few whiffs of an inhalation anæsthetic are not noticed. Morphine is not used before operation and there is rarely vomiting or sweating during operation. By removing the mask during operation the patient can be roused to talk or swallow, if desired. After operation he lies quietly in any position in which he is placed, sleeps normally, or is quite apathetic but can be roused to drink. The reflexes, importantly the cough and gag reflexes, are not interfered with. This effect lasts ordinarily from 12 to 24 hours—in one case as long as 56 hours. Sharp pain will rouse the patient, as it will from normal sleep, and for such pain we give morphine, but the aches, the vague general discomfort, and the sense of frightened confusion that are the common sequelæ of all surgical procedures do not disturb these patients. On the day after operation, they rarely recall anything of the events of the previous day—going to the operating room, inhalation of anæsthesia, postoperative dressings, physician's examinations, or even the faces of the special nurses who came on duty just before operation.

The last 164 cases in which this method was used have been analyzed and reported in detail. Of those who had luminal in one dose, it is interesting to note that 74 per cent of the thyroidectomies (the great majority being toxic) and 45 per cent of other major operations were accomplished with nitrous oxide alone with an ease hitherto undreamed of for this gas; 70 per cent of those having luminal in one dose did not vomit during or after operation; and 53 per cent did not require morphine in the first 24 hours after operation. There were no significant changes in blood pressure, pulse, or respiration. Except in those patients who were put on a peritonitis regimen as a precaution after operation, hypodermoclysis was rarely used, the absence of nausea allowing the patients to drink freely. Sweating was rarely seen and we have never known such freedom from postoperative respiratory complications.

The dose of luminal varied from 12 to 30 grains given in one dose, as is now our routine. This plan has no place, of course, in patients who have much gastric retention or in those who are vomiting for any reason and in whom fluid by mouth is contra-indicated. One should be cautious in the use of luminal in conjunction with spinal anæsthesia, for the combined effect may cause sufficient drop in blood pressure to be temporarily embarrassing. We have experienced this only once; moreover, a patient, uncertain of his balance and not able to co-operate thoroughly, might conceivably make a sudden movement and cause breaking of a needle. Patients entering the hospital are tested for individual idiosyncrasy by small doses of luminal. In a few cases there was a very transient skin rash as the only toxic manifestation. The economic saving to a patient who is not vomiting, excitable, suffering, or disturbing his neighbors is reflected by a lessened demand on nursing service.

We have found a wide field of usefulness for this procedure. With a routine dose of 1½ grains of luminal (for *non-thyrotoxic* individuals) and nitrous oxide, occasionally supplemented by a few whiffs of ethylene during packing off, cholecystectomy and other procedures down to the hysterectomy level (where we ordinarily prefer "spinal") are readily accomplished. A moderate amount of abdominal exploration is entirely feasible. The radical breast amputation furnishes an excellent opportunity also. Certainly in the case of thyroid surgery the manifold advantages of the "luminal effect" are at their best. It is useful in the minor anal and rectal operations where one has been used to particularly deep anæsthesia.

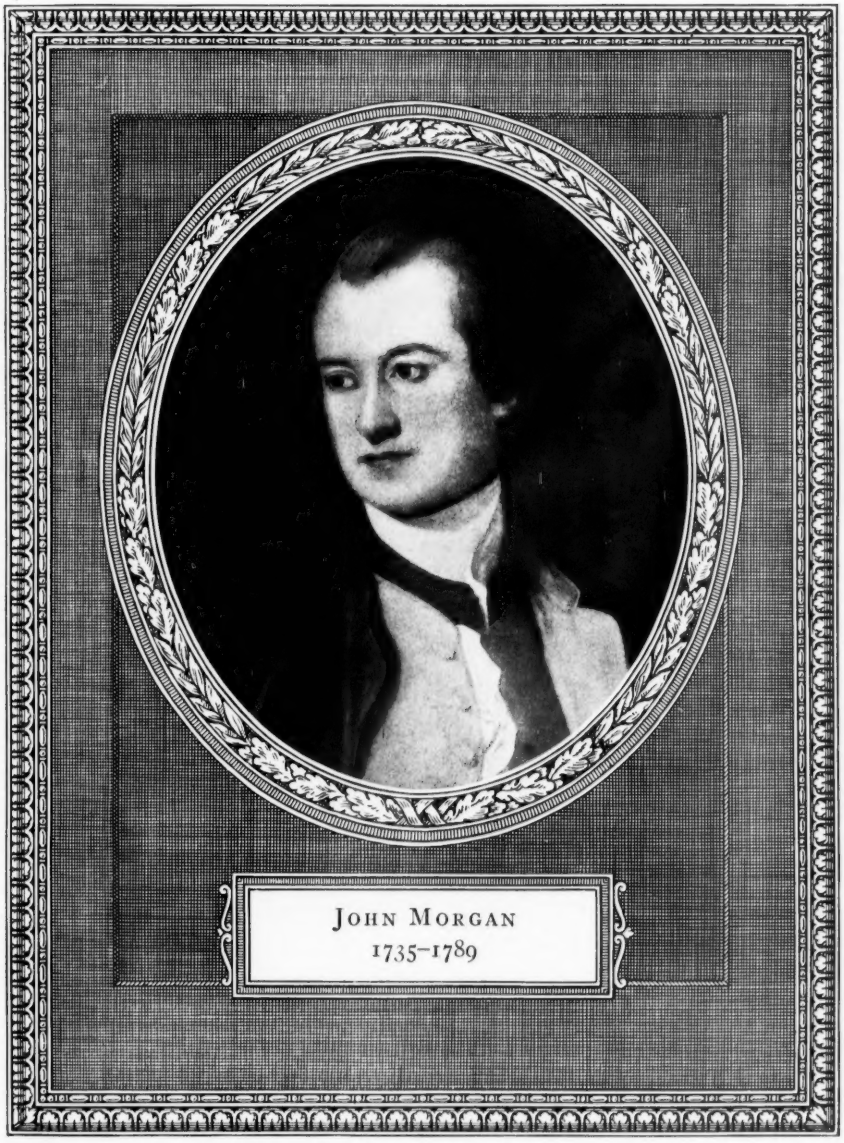
But beyond all figures and an author's enthusiasm, the court of last resort is the feeling of a patient who has experienced this "semi-anæsthesia" after previous operation under different methods. His enthusiasm for it makes even a casual visitor realize how nearly completely the dreads of a surgical patient can be removed. WILLARD BARTLETT.

MASTER SURGEONS OF AMERICA

JOHN MORGAN

JOHN MORGAN, who was not a surgeon, was important in the history of American surgery because of his pioneer status as a medical educator and founder of our first medical school and because he was physician in chief and director general of the hospital in the Revolution, a position corresponding to that of the surgeon general of the Army at the present time.

He was born in Philadelphia in 1735, the son of well-to-do parents, Evan and Joanna (Biles) Morgan. He was first sent to school to Rev. Dr. Finley's Nottingham Academy, where he received the classical training for which the place was famous, and then to the College of Philadelphia, where he graduated in the first class to be granted literary honors, that of 1757. During the last years of his college course, he took up the study of medicine under Dr. John Redman. With the medical education derived from this apprenticeship, he became a surgeon, as well as a lieutenant of the line, in the French and Indian War in 1758, being attached to Forbes' expedition against Fort DuQuesne. In 1765 he spoke of having had four years of military experience but it is impossible to see how this could have been so. In 1760 he left the army and sailed to Europe to continue his studies in medicine. In London he worked under William Hunter for a year and then spent two years in Edinburgh, where he was given the M.D. in 1763. From Edinburgh he went to Paris and there spent a winter in the study of anatomy. Thereafter he made the grand tour, calling upon and being warmly received by Morgagni and Voltaire. His journal covering this tour has been published and it reveals the young man taking his sightseeing and art very seriously and systematically. He was made corresponding member of the Academy of Surgery of Paris, a Fellow of the Royal Society, licentiate of the College of Physicians of London, and member of the College of Physicians of Edinburgh. During his residence abroad he planned with William Shippen the founding of a medical school in Philadelphia, and upon his return there in 1765, armed with a strong letter from the proprietor, Thomas Penn, he proposed the establishment of a medical school in connection with the College of Philadelphia (University of Pennsylvania). The idea was approved and he was elected professor of theory and practice of physic, and Shippen was given the professorship of anatomy and surgery. The new school prospered and it has always been one of the leading schools of America.



JOHN MORGAN
1735–1789

Before he left England and again in Philadelphia, Morgan wrote that he would attempt the practice of medicine without dispensing his own drugs or practicing surgery, and there is no evidence that he ever did either, except that he attended the wounded on the battle field. He brought from England an apothecary to whom he sent his prescriptions.

In October, 1775, Dr. Morgan was appointed director general and physician in chief to the hospital, in succession to Dr. Benjamin Church, who had been detected in correspondence with the enemy. Morgan at once repaired to Cambridge, where he assumed the duties which so nearly overwhelmed him for the next fifteen months. Morgan had trouble with Dr. Stringer, director of the Hospital of the Northern Department, with Dr. Shippen, director of the Hospital of the Flying Camp in New Jersey, and with the regimental surgeons and officers, who felt that he was negligent of their needs and opposed to their interests. Congress also, influenced by complaints, showed itself hostile to him and eventually, in January, 1777, it dismissed him and Dr. Stringer without trial, and a few months later it promoted Dr. Shippen to the position of director general. Dr. Morgan at once began to beseech Congress for vindication. This Congress granted in June, 1779, in a resolution which declared that he "did conduct himself ably and faithfully in the discharge of his office," but it did not reappoint him to the office. Meanwhile Morgan was joined by Benjamin Rush, James Tilton, and perhaps others, in making charges against Shippen. Shippen was brought to trial in 1780 and was honorably acquitted. Morgan's accusations against him were doubtless motivated in part by chagrin, while the writings of Rush and Tilton show them both to have been men of acrid humor and hearty dislikes. Such was the disorganization, poverty, lack of transportation, low state of discipline in the Army, such the jealousy between colonies and communities, such the lack of preparation for war and the ignorance and indiscipline of the people, such the meddlesomeness of Congress and its neglect of the Army, that it may be that nobody could have been more successful as director general of the hospital in 1776–7 than was Morgan. As a matter of fact, Washington's success with the Army of that time was little better. Nevertheless, Morgan's "Vindication of his Public Character," written by himself and published in Boston in 1777, does permit the inference that, despite the evils with which he had to bear or to contend, he might have accomplished more except for drawbacks due to his own personality. These faults were apparently two: first, an inability to delegate work, which was not wholly compensated for by the hardest of work on his own part, and second, a mistaken or too modest conception of his duties as director general. The individual regiments at first brought their own medical men, and Washington found the need at Cambridge to be for a general hospital service. Congress legislated for that, but not, as Morgan viewed the matter, for any regimental service; whereas the regiments and apparently the States, and possibly

Congress itself, expected him to make provision for all medical necessities. Had Morgan boldly taken this same view and regarded himself as the one responsible for all medical service, he might have had greater support from the regimental officers, line as well as medical, and so had greater success. As it was, he regarded himself as having to do only with "The Hospital" and not with the regiments; he was unable to furnish these with necessary supplies; the regimental surgeons thought him negligent of, and opposed to, their needs and they worked against him. From their enmity arose a large part of his troubles.

Another large part came from the promotions of Stringer and Shippen, due partly to politics, possibly in part to the machinations of the two, but possibly also in part to Morgan's too great concentration on the work in his immediate vicinity, with consequent inability to look after the service of distant forces in any effective manner.

As a young man, Morgan was admired and copied, he had his place among the intellectual elite of the city, he was sufficiently untrammeled by custom to be able to avoid surgery and the dispensing of drugs, things which all other American physicians did. He could even indulge in the then foppish peculiarity of carrying a silk umbrella.

After his military service he wrote nothing except his "Vindication" and he largely retired from the public gaze, although continuing to practice and to teach. He died at Philadelphia on October 15, 1789.

He was a learned man, a delightful personality, possibly an excellent administrator, certainly a hard worker, but his army service came at a time when success in it was all but impossible, when Washington himself was meeting with every kind of defeat and discouragement. But he is one of the great figures in American medical education. His published writings are: (1) De Puopiesi, sive Tentamen Medicum Inaugurale de Puris Confectione. Edinburgh, 1763. 55 pp. (2) Discourse upon the Institution of Medical Schools in America. Philadelphia, 1765. 91 pp. 12 mo. (3) A Recommendation of Inoculation, according to Baron Dimsdale's method. Boston, 1776. 18 pp. (4) A Vindication of his Public Character in the Station of Director-General of the Military Hospitals, and Physician in Chief to the American Army, Anno 1776. Boston, 1777. 158 pp. (5) The Journal of Dr. John Morgan. Lippincott, Philadelphia, 1907. 259 pp.

P. M. ASHBURN.

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Vin Medityinæ medullam, nôsse. SENNERTVM *vide*
Ora sic lulit, parem qui vix habet laude ingenî.
CAR SPONIVS D.M.

THE SURGEON'S LIBRARY

OLD MASTERPIECES IN SURGERY

ALFRED BROWN, M.D., F.A.C.S., OMAHA, NEBRASKA

THE WORKS OF DANIEL SENNERT

DANIEL SENNERT was a contemporary of Cæsar Magatus and one of his most severe critics and bitter opponents. He belonged to the school which admitted no change from the ideas of the ancients and bitterly opposed anything which had to do with progress beyond the established routine. A believer in the supernatural and in alchemy, recommending to his colleagues and students the study and employment of astrology, and imbued with a belief in the origination of disease in witchcraft and magic, he could hardly be expected to be an unbiased observer and practitioner who would accept new methods or even consent to try them out. His first impulse would be to condemn them heartily.

Sennert was a German who received the best in education that his country afforded but went no farther than Switzerland to obtain outside information. Consequently, he would naturally be more or less narrow in his beliefs and viewpoints. He was born in Breslau in 1572. His education he obtained in Wittenberg, Leipzig, Jena, Frankfort on the Oder, and finally in the University of Basle. Then he returned home and began to practice and teach. He was appointed professor of medicine and served six terms as Rector of the university. It followed from his preeminence in medical and university affairs that he was appointed physician in ordinary to the Elector Johann Georg of Saxony. He died of the pestilence in 1637.

Sennert never wrote a book devoted to surgery alone. It is doubtful whether he ever practiced it actively. He was nevertheless well grounded in surgical theory and knew, not only the beliefs and practices of the ancient authors, but also those of his contemporaries and those who had shortly gone before. He shows that he was acquainted with the works of Dalla Croce and Fabricius of Acquapendente in Italy, Paré in France, Fabricius Hildanus in Germany, and Pieter Paaw in Holland; in other words the authors of the surgical classics of the time. These he knew as a bystander on the side lines as it were, but with his aloofness he nevertheless could not resist the opportunity to mix into the most active surgical squabble of the period and in fact became one of the principals in it. In 1611, he published his *Principles of Medicine and concerning the origin of the Living Principles in Brutes.* This went through several editions and the second section of its fifth book is devoted to the type of surgery noted above.

Later, in 1616, Cæsar Magatus published his work on wounds which aroused Sennert's antagonism and in his *Opera Omnia* published in three great folio volumes at Leyden in 1650, one finds the fifth book beginning with the fourth part discussing the question of wounds. After describing the various types of wounds, their complications, and the primary treatment of uncomplicated as well as complicated wounds of various types to which he devotes eight chapters, Sennert finally comes to grips with Magatus on his new method of treatment of wounds with infrequent dressings. He heads the chapter "A judicial inquiry concerning the method of curing wounds of Cæsar Magatus and Ludovic Septalius," and concludes the first paragraph after stating that Magatus had brought out a new treatment which differed from that of the ancients by saying "Ludovic Septalius in his eighth book of medical considerations praises, commends, and defends Cæsar Magatus and thinks he deserves praise both for advancing the study of the art of medicine and for freeing the sick from a disagreeable cure. And I do not think that I am injuring the public welfare if I, being of a different opinion, propose to discuss that opinion in this place." The arguments that Sennert advanced to prove Magatus wrong are long and wordy but always can be boiled down to one—that the ancients never treated wounds the Magatus' way and their patients did fairly well. Hence, why change? Magatus could not resist an answer but could not make it over his own name for he was a cleric and mundane quarrels were not for him. So he published his answer as if written by his brother Jean Baptiste and reiterated all his arguments against frequent dressings and the use of tents and added a few new ones. He neglected to set down any definite rules when dressings should be changed.

The argument augmented interest in wound treatment if it did nothing else and whenever interest is aroused in a medical or surgical subject more efficient therapy follows. So Sennert, though primarily mostly interested in internal medicine, through his contentiousness accomplished much for surgery by bringing the subject of wound treatment prominently before the profession.

REVIEWS OF NEW BOOKS

IN presenting the third edition of a two volume work on pediatric surgery, Kelley[1] aptly states that "there should be children's surgeons as well as children's physicians, or 'if one objects to cutting up surgery into little pieces,' as Timothy Holmes says, it should at least be required that the surgeon extend his knowledge to pediatrics." The author understands the psychology of the child and beautifully expresses the relationship between physician and little patient. On the whole, the work is well arranged and presented but is a work for general rather than specific reference.

In the consideration of general subjects in the first chapter, various laboratory examinations are discussed, but nothing is said of blood chemistry and the importance of stereoroentgenography. The section on postoperative care and on blood grouping and the various methods of transfusion in relation to hæmorrhage and its control is very good.

The author, in discussing the surgical treatment of hyperthyroidism, makes the statement that "thyroidectomy should generally be preceded three or four months by ligation of the superior thyroid arteries, one at a time, some days or a week apart. Severe reaction may be looked for after each of these procedures." This advice since the introduction of iodine premedication by Plummer may be strongly contested. Multiphase operations are being abandoned even by such vigorous exponents as Lahey and Crile.

In the discussion of rickets, one can hardly accept the statement that there is a "predisposition to general convulsions upon the slightest provocation," and further that "vitamin A is the curative factor." Unfortunately the rôle of antirachitic vitamin D and the use of the irradiated sterols is omitted. The section on infantile scorbutus makes no mention of antiscorbutic vitamin C.

The treatment of burns is excellently written, emphasis being placed on the tannic acid method and on the importance of the extension position in healing with early skin grafting.

Early surgical interference in acute osteomyelitis and later sequestrotomy are correctly urged. In the discussion of tuberculosis of bones and joints, the author aptly states that "in local treatment, there is to be no resort to any operative measures unless all other means have been exhausted; and then there is not to be in the case of any growing child an operation which mutilates, or which destroys the epiphyseal lines of growth. . . . Secondary infection must be avoided. . . . Rest is the most important of all agencies for local treatment . . . and all other means sink into such minor positions as to be almost negligible when compared with rest."

The sections dealing with hydrocephalus and intracranial birth hæmorrhages are excellent. A very complete discussion of intubation in laryngeal diphtheria appears in volume ii.

The omission of bronchiectasis from the section on surgery of the thorax is regrettable. Its importance in relation to swallowed foreign bodies, pertussis, and other respiratory infections should have been emphasized. Of 32 operative cases listed by Lilienthal in his text 17 patients were 16 years of age or younger.

In the treatment of peritonitis in general the author advises emptying the bowels by the use of calomel and salines. "Pain and tenderness can be greatly relieved by smearing the abdomen with extract belladonna, one drachm, to glycerin, one ounce under oil silk." Such statements are reminiscent of the medicine of a long past day. The repeated reference throughout this text to the use of calomel and the salines in the acute infections can hardly be accepted by the reviewer, who has never had occasion at any time in his practice to employ these drugs.

Anomalies of the bile passages which are not infrequently seen in the early jaundice and death of infants are not mentioned, nor is there a section on the liver or pancreas.

As a text devoted to the general surgery of children, the work is commended to the profession.

I. MICHAEL LEVIN.

THE entire subject of gynecology is presented by Kelly[2] in a relatively complete 1,000 page volume. This book is well organized and beautifully illustrated. The newer diagnostic aids, the tubal patency test, lipiodol, pneumoperitoneum, etc. and recent work on internal secretion are well presented.

The recent advances in gynecology, adenomyoma, radium therapy, diathermy, ureteral stricture, and electric cautery are discussed.

Kelly's own work comprises the larger portion in this volume. He has selected as collaborators such men as Ward, who beautifully describes plastic surgery.

Burnham's chapter on radium in carcinoma of the uterus merits special note. This volume deserves a place in the library of everyone who is interested in gynecology or pelvic surgery.

EUGENE A. EDWARDS.

[1] SURGICAL DISEASES OF CHILDREN; A MODERN TREATISE ON PEDIATRIC SURGERY. By Samuel Walter Kelley, M.D., LL.D., F.A.C.S. Vols. i and ii. St. Louis: The C. V. Mosby Company, 1929.

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